



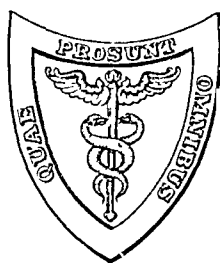
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ORIGINAL ARTICLES.

KIDNEY FUNCTION.<sup>1</sup>

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THE subject of this paper, kidney function, is far too broad for discussion within the permissible limits of one lecture. I therefore propose to restrict what I have to say to the subject:

**Glomerular Function and the Modes of its Regulation.**—What I have to present is based upon work which has been proceeding with interruptions in the laboratory of pharmacology of the University of Pennsylvania for a number of years past; this work has been jointly carried on by Dr. O. H. Plant and myself during the years 1915 to 1920 and by Dr. Carl F. Schmidt and myself from September of last year until now. Their collaboration has been invaluable.<sup>2</sup>

*I. Evidence that the Glomerulus of the Kidney is the Chief Structure Concerned in the Renal Elimination of Fluid from the Blood.*—Until the classical work of the English anatomist William Bowman, published in 1842, there was no convincing evidence that connection existed between the Malpighian bodies and the uriniferous tubules. By extraordinary skill in dissection, Bowman proved that the capsule of the Malpighian body is the expanded extension of the membrane of the tubule. His first identification of the complete unit of structure by which urine is formed must therefore be regarded as the beginning of modern study of renal function.

<sup>1</sup> A lecture delivered before the Harvey Society, New York, February 26, 1921.

<sup>2</sup> The results of this work will shortly be published in the American Journal of Physiology.



Appended to Bowman's very complete description of the vascular arrangements of the kidney is a theory of the parts played by tubule and glomerulus in the formation of urine. He laid emphasis upon the structural similarity of the epithelium of the tubules and that of secreting glands, and drew the inference that the tubules eliminate from the blood "the peculiar principles found in the urine." He laid equal emphasis upon the dissimilarity of structure of tubules and capsule, and stated his conception of the significance of this dissimilarity in these words, which, though frequently quoted, may well be repeated:<sup>3</sup>

"Thus the Malpighian bodies are as unlike as the tubes passing from them are like the membrane, which, in other glands, screens its several characteristic products from the blood. To these bodies, therefore, some other and distinct function is with the highest probability to be attributed. The peculiar arrangement of the vessels in the Malpighian tufts is clearly designed to produce a retardation in the flow of blood through them. . . . It would indeed be difficult to conceive a disposition of parts more calculated to favor the escape of water from the blood than that of the Malpighian body. A large artery breaks up in a very direct manner into a number of very minute branches, each of which suddenly opens into an assemblage of vessels of far greater aggregate capacity than itself, and from which there is but one narrow exit. Hence must arise a very abrupt retardation in the velocity of the current of blood. The vessels in which this delay occurs are uncovered by any structure. They lie bare in a cell from which there is but one outlet, the orifice of the tube. This orifice is encircled by cilia in active motion directing a current toward the tube. These exquisite organs must not only serve to carry forward the fluid already in the cell, and in which the vascular tuft is bathed, but must tend to remove pressure from the free surface of the vessels, and so to encourage the escape of their more fluid contents. Why is so wonderful an apparatus placed at the extremity of each uriniferous tubule if not to furnish water to aid in the separation and solution of the urinous products from the epithelium of the tube?"

This is the first suggestion, founded, it is true, upon teleological argument from structure, that the glomerulus is the chief site of fluid elimination in the kidney. This suggestion developed into universal belief. The experiment which established its truth was not made until 1878, when Nussbaum<sup>4</sup> performed the operation in frogs of ligation of the renal arteries. This excluded the glomeruli from the circulation, but, owing to the double blood supply of the frog's kidney, did not abolish circulation in the vessels of the tubules. The result of this ligation was cessation of urine elimination.

<sup>3</sup> Phil. Tr. Roy. Soc., 1842, pp. 74 and 75.

<sup>4</sup> Arch. f. d. ges. Physiol., 1878, 16, 139; 1878, 17, 580.

This observation, confirmed by others,<sup>5</sup> nearly approaches to direct proof of the assumption made by the older anatomists. Since it is completely in harmony with considerations of structure, since it is supported by a mass of less direct evidence obtained in other ways, and since there is no opposing evidence, so far as I am aware, we may regard this question, so fundamental to all further study of kidney function, as satisfactorily settled.

*II. The Nature of the Process by which Fluid is Separated from the Blood in the Glomerulus.*—In Bowman's statement of his hypothesis that the glomerulus separates water from the blood, no clear idea is given of the nature of the process. Unaware of the epithelium which covers the glomerular tuft, he regarded the capillaries as projecting naked into the capsule, and he speaks of the cilia at the orifice of the tubule as presumably having power of diminishing pressure on the capsular side of the capillary tuft and so facilitating escape of fluid from the blood. It seems to me that his words vaguely indicate the escape of fluid because of pressure within the capillary vessels.

There is no such vagueness, however, in Carl Ludwig's statement, made in 1844, of his conception of the process.<sup>6</sup> Using the anatomical facts demonstrated by Bowman and confirmed by himself, and applying principles of hydraulics, he stated that a significant pressure must be exerted by the blood within the glomerular capillaries upon their walls, and that this pressure must result in the filtration of a certain amount of fluid through them. He assumed that the membrane through which the fluid passed was normally impermeable to proteins, to fats and to salts which might be combined with these, and hence that the urine as formed in the glomerulus is a protein-free filtrate containing blood crystalloids in the proportion in which they exist free in the blood.

I have no wish to enter in great detail into a discussion of the evidence for and against the filtration theory; it has been adequately reviewed many times and forms part of current physiological teaching. Since in the development of what is to follow an appreciation of the chief elements of strength and of weakness in the filtration theory is necessary, I make no apology for briefly presenting the most important facts. The question whether the glomerulus filters fluid or secretes fluid is more than academic. A well-based conviction that the understandable process of filtration is the chief factor of glomerular activity permits clearly defined views concerning the nature of alterations in glomerular function which occur in health and disease. It carries with it as an inevitable corollary a conviction of reabsorption of both water and dissolved substances

<sup>5</sup> Adami: Jour. Physiol., 1885, 6, 582. Beddard: Ibid., 1902, 28, 20. Cullis: Ibid., 1906, 34, 250. Bainbridge, Collins and Menzies: Proc. Roy. Soc. B., 1913, 86, 355.

<sup>6</sup> Wagner's Handwörterbuch der Physiologie, 1844, 2, 637.

from the lumen of the tubule, for no other process could account for the difference in composition between a blood filtrate and the urine as it leaves the kidney. Absence of such conviction, on the other hand, necessitates refuge in the conception of "secretion," a word implying ignorance or uncertainty of processes involved and an ill-defined point of attack on the further questions of alterations in renal function.

There are three groups of experiments which, I think, form the chief support of the filtration theory.

First, experiments which demonstrate the parallelism between urine elimination and renal blood-pressure. These include the experiments in Ludwig's laboratory by Goll,<sup>7</sup> showing that changes in general arterial blood-pressure, induced by vagus stimulation, hemorrhage, injection of blood or ligation of large arterial trunks caused changes in a similar sense in urine flow; and those by Hermann,<sup>8</sup> in which diminution in urine was found to follow partial obstruction of the renal artery. They include also numerous experiments which developed from Claude Bernard's discovery of vasomotor nerves, experiments in which the nerve supply of the kidney was either divided or stimulated, and resulting increase or decrease in urine found to be attributable to dilatation or constriction of the vessels in the kidney.<sup>9</sup> It was recognized by Ludwig and his colleagues that such changes in the renal circulation as were studied in these experiments involved alterations not only in renal blood-pressure but in velocity and volume of renal blood flow as well. Reasons were adduced (Hermann) for belief that the effective variable in these experiments was that of pressure. The force of the experiments and the influence of Ludwig were such that his conception of glomerular filtration and tubular reabsorption became the generally accepted view.<sup>10</sup>

The second group of experiments to which I refer is based upon this principle of physics: that in order to separate a dissolved substance from its solvent by filtration through a membrane, permeable by the solvent but not by the dissolved substance, filtration pressure must be greater than the osmotic pressure of the dissolved substance. Tammann,<sup>11</sup> of Rostock, in 1896 showed that the osmotic pressure of all the substances dissolved in the blood plasma was nearly eight atmospheres (5840 mm. Hg.); that the osmotic pressure of the organic solids of blood plasma amounted to 840 mm. Hg. (He regarded the osmotic pressure of proteins as negligible.)

<sup>7</sup> Ztschr. f. rat. Med., 1854, 4, 78.

<sup>8</sup> Sitzungsber. d. kais., Akad. d. Wiss., Wien, 1862, 45, 2, 317.

<sup>9</sup> Bernard: *Leçons sur les propriétés physiologiques des liquides de l'organisme*, 1859, 2, 169. Eckhard: *Beitr. z. Anat. u. Physiol.*, 1869, 4, 155. Ustimowitsch: *Ber. u. d. Verh. d. k. Sachs. Gesell. d. Wiss. z. Leipzig (Math.-phys. Cl.)*, 1870, 22, 430. Grützner: *Arch. f. d. ges. Physiol.*, 1875, 11, 370.

<sup>10</sup> Cf. Heidenhain: *Hermann's Handbuch der Physiologie*, 5, 1, p. 318.

<sup>11</sup> Tammann: *Ztschr. f. physikal. Chem.*, 1896, 20, 180.

Since no pressures of this order of magnitude are to be found in the animal circulation, he concluded that the only substances of plasma which could physically be held back in the glomerulus are the proteins; hence the fluid separated in the glomerulus must be the water of the blood containing all dissolved substances except proteins.

Starling,<sup>12</sup> in the same year, discovered that the osmotic pressure of plasma proteins amounted to from 30 to 40 mm. Hg. He showed that a force of this magnitude exerted by substances retained within the bloodvessels was sufficient to explain in part the absorption of fluid from tissue spaces into the bloodvessels. In 1899 he extended this reasoning to the explanation of glomerular function.<sup>13</sup> By improved method he redetermined the osmotic pressure of plasma protein and obtained the figure 25 to 30 mm. Hg. If the osmotic pressure of plasma protein is the force which blood-pressure must overcome in order to filter fluid from the blood in the glomerulus, then it should be found that the lowest arterial blood-pressure compatible with urine elimination should be slightly above this. His own experiments and those of many others showed that urine ceased to be eliminated when arterial pressure fell below 40 mm. Hg. Further, if glomerular function is filtration then the difference between arterial blood-pressure and the maximum pressure in the ureter against which urine can be eliminated should be almost that of the osmotic pressure of the proteins. He found this difference during profuse diuresis in the dog to be 32 to 43 mm. Hg. These results, confirmed and extended by Knowlton,<sup>14</sup> are so completely in accord with the demands of the filtration theory that they furnish the strongest support for it.

The third group of experiments in this connection are those of Barcroft and Straub<sup>15</sup> made in 1910. They applied to the kidney the methods so fruitfully developed by Barcroft for estimating the rate of metabolism of organs. Saline diuresis—*i. e.*, diuresis following injection of sodium chloride solutions—was found to be unaccompanied by increase in utilization of oxygen or formation of carbon dioxide. Knowlton and Silverman<sup>16</sup> later showed that this was true for diuresis following injection of pituitrin. The conclusion was drawn that physical factors rather than "vital" or "secretory" are concerned in this increase in kidney function, the inference being that filtration is increased.

These are the facts which to my mind most nearly constitute "proof" of the filtration idea: they are reinforced by considerations of the structure of the glomerulus and by observations in other directions; that the more rapidly urine is eliminated the more nearly it comes to resemble a filtrate from the blood; that the

<sup>12</sup> Jour. Physiol., 1896, 19, 312.

<sup>14</sup> Ibid., 1911-12, 43, 219.

<sup>16</sup> Am. Jour. Physiol., 1918, 47, 1.

<sup>13</sup> Ibid., 1899, 24, 317.

<sup>15</sup> Ibid., 1910-11, 41, 145.

glomerular fluid is alkaline, as tested by intravital indicators; that the osmotic pressure and chloride content of the cortex more closely resemble that of the blood than does that of the medulla. This collection of facts led Bayliss to write, in 1915, "The evidence for this (glomerular filtration) is overwhelming;"<sup>17</sup> and Cushny, in his development of the "modern" theory of urine formation, to accept glomerular filtration as a fundamental truth.<sup>18</sup>

It is easy to develop conviction of the truth of filtration by study of the work to which I have alluded. It is not so easy to hold it after consideration of some of the questions which have been put to the filtration theory and have not found satisfactory answer.

Heidenhain, in 1874, began the publication of his work on the kidney, from which developed the so-called Bowman-Heidenhain theory. As is well known he injected indigo carmin into the circulation and failed to find traces of it in the capsule or any staining of glomerular structures by it. Since it was to be found in the lumen of the tubule, and since the tubular epithelium was stained by it, he was forced to conclude that it had been secreted by the tubules and had not been filtered by the glomerulus.<sup>19</sup> This observation led him to further results which obliged him to deny the filtration-reabsorption theory completely and to attribute urine formation to secretory processes in the epithelium of glomerulus as well as of tubule—i. e., to processes not explainable by known physical or chemical laws.

Most of Heidenhain's contentions have since been successfully met by adherents of the filtration idea. Cushny's monograph contains an admirable exposition of this subject. One objection, however, seems to me to have been least satisfactorily answered, and it happens that this is the one to which Heidenhain himself attached the most weight. It concerns the effects of compression of the renal vein upon urine elimination. The following is a translation of his own words.<sup>20</sup>

"But if mechanical filtration does really occur, then elimination of water must always increase with the pressure. An old experiment shows that this is not so. For if the pressure in the glomeruli is increased by partial or complete occlusion of the renal vein an immediate diminution in urine occurs.

"This fact contradicts the pressure hypothesis in the most abrupt (schroffstem) manner. . . .

"If it is considered that increase in aortic pressure, if only a few millimeters, often causes a considerable increase in urine, and that after partial or complete occlusion of the renal vein a considerable rise of pressure within the glomerular vessels must occur, then it is

<sup>17</sup> Bayliss: Principles of General Physiology, 1915, p. 355.

<sup>18</sup> Cushny: The Secretion of Urine, 1917.

<sup>19</sup> Heidenhain: Arch. f. mik. Anat., 1874, 10, 1.

<sup>20</sup> Heidenhain: Hermann's Handbuch der Physiologie, 1883, 5, pt. 1, pp. 321, 325.

apparent that here is a phenomenon completely inexplicable by the filtration hypothesis."

Ludwig<sup>21</sup> was aware of this objection and had met it by demonstrating that complete obstruction of the renal vein in the living animal caused such swelling of the veins within the kidney that the tubules were compressed and their lumina obliterated. Obviously, no urine could issue from the kidney under these circumstances. It appears that Heidenhain<sup>22</sup> accepted Ludwig's demonstration of the effects of complete occlusion, but he did not regard it explanatory of the events which follow partial closure of the vein. Slight obstruction of a degree sufficient to lessen but not to suppress urine flow could not cause such lessening by engorgement of veins with resulting closure of tubules. The fact that urine continued to flow, though at a lower rate, indicated that the tubules were patent. Paneth's<sup>23</sup> later experiments, showing the possibility of diuresis by sodium nitrate during constriction of the renal vein, confirmed this conclusion. For this reason Heidenhain regarded the failure of slight compression of the renal vein to increase urine flow as the strongest argument against the filtration hypothesis, and it was this that led him to the belief that the velocity of blood flow through the glomerulus, rather than the pressure of blood within it, was the determining factor in the first formation of urine in the kidney.

In answer to this objection it was pointed out by Tammann<sup>24</sup> that if fluid is filtered from the blood in the glomerulus any stagnation of flow in the glomerulus, as by venous obstruction, would lead to rapid increase in osmotic resistance to filtration. It has not been shown that this factor can be so effective during partial occlusion of the vein as to more than compensate for the increased glomerular pressure. It has been suggested by De Souza<sup>25</sup> that blocking of the renal vein causes reflex constriction of the renal artery, but no evidence of this has been presented so far as I am aware. Consideration of these matters leads me to think that the argument against filtration, based upon the effects of obstruction of the renal vein, has not been adequately answered.

Another series of obstacles in the way of unreserved acceptance of the filtration hypothesis has arisen from the comparison of urine elimination with vascular conditions in the kidney, as shown by oncometer records of kidney volume, and these difficulties have increased with the later development of improved methods of estimation of the flow of blood through the kidney.

The oncometer, first applied to the study of renal physiology by Roy and Cohnheim in 1883, registers changes in the total volume of the kidney; these changes are commonly referred to alterations in

<sup>21</sup> Sitzungsber. d. k. Akad. d. Wiss. zu Wien, November, 1883.

<sup>22</sup> Hermann's Handbuch, 5, 1, p. 317. Cf. also Paneth, pp. 550, 551.

<sup>23</sup> Arch. f. d. ges. Physiol., 1886, 39, 515.

<sup>24</sup> Loc. cit.

<sup>25</sup> Jour. Physiol., 1900-01, 26, 139.

the state of the renal bloodvessels. In 1900 and 1901 Gottlieb and Magnus<sup>26</sup> made an admirable series of observations on blood-pressure, kidney volume and urine flow during diuresis. Following the injection of single doses of diuretics, remarkable parallelism between urine elimination and vascular dilatation, as shown by the oncometer, was observed; but when repeated dosage was given this parallelism failed. Diuresis was observed to increase in some instances at a time when renal vessels, as shown by the oncometer, were constricting; in others it diminished while renal vessels were similarly shown to be dilating.

These objections were materially supported by the late Professor Brodie, of Toronto. He extended the observations of Magnus and Gottlieb by including in his experiments direct estimations of blood flow through the kidney. In his lecture before the Harvey Society in 1910<sup>27</sup> and in his Croonian lecture of 1911<sup>28</sup> he stated that, following the injection of diuretics, in five experiments he had observed the following coincident phenomena: Increased kidney volume (indicative of dilatation of vessels); diminished blood flow (indicative of constriction of vessels); increased urine elimination.

Both Magnus and Brodie apparently accepted the common implication of vascular changes, namely, that dilatation of renal vessels means rise of intraglomerular pressure, and constriction of renal vessels means decrease in intraglomerular pressure; and hence their observations became so self-contradictory when viewed in the light of the filtration hypothesis that they were forced to abandon it.

In the considerations thus far advanced I have hoped to show that in spite of the array of strength back of the belief that urine is first formed in the glomerulus by a process of filtration, sound observations exist, made by most competent observers, which have forced them to deny it. Concern over these difficulties, and the necessity of a conviction concerning them, led to a series of experiments by my colleagues and myself which have, we think, a direct bearing on their solution.

In Hermann's<sup>29</sup> second paper on kidney function, published in 1862, it is stated that "The effect of pressure changes as compared with other factors which modify urine excretion can only be brought out clearly when one has control over the blood entering the vascular system and can regulate it at will." I cite this to show that the desire for some sort of artificial experimental control over circulatory conditions in the kidney in order to reduce the number of variables in an experiment is very old. Hermann devised a clamp by which the caliber of the renal artery could be narrowed, hoping to identify the effects of lowered renal blood-pressure by this means; somewhat

<sup>26</sup> Arch. f. exp. Path. u. Pharm., 1901, 45, 223.

<sup>27</sup> Harvey Lectures, 1909-10, 5th series, p. 81.

<sup>28</sup> Brodie: Proc. Roy. Soc., B., 1913-14, 87, 571.

<sup>29</sup> Loc. cit.

similar experiments have more recently been made. A defect in such experiments, recognized by their authors and emphasized by Heidenhain, is that such a device simultaneously alters both blood-pressure and blood flow in the renal circulation, and there is no direct means of distinguishing effects due to one of these to the exclusion of the other.

During the years 1912-14, C. K. Drinker and I designed and constructed an apparatus for the perfusion of isolated surviving organs capable of pumping a pulsating stream of fluid in a manner similar, as pulse records showed, to that of the heart.<sup>30</sup> Its volume output was controllable within fairly wide limits. With it we perfused the dog's kidney and were able to show that the fluid which issued from the ureter was urine and not a transudate. In 1914-15 Dr. O. H. Plant and I elaborated a method for perfusing the rabbit's kidney *in situ* with this apparatus.<sup>31</sup> Our method possessed these advantages and possibilities:

1. The perfusion fluid was the undiluted blood of the animal whose kidney was perfused plus blood taken fresh from another animal of the same species. Hirudin was used to prevent clotting.

2. The artificial circulation through the perfused kidney was inaugurated without any interruption in blood flow through the organ, and in some instances urine flow continued without interruption during the change from normal to the artificial circulation.

3. While the output of the perfusion apparatus could be varied at will, for any particular adjustment the output was constant, regardless of the resistance offered by the vessels through which it drove the blood. It was thus possible to alter pressure by various means within the kidney vessels without simultaneous alterations in volume flow or velocity of blood in them. It is in this respect that our experiments differed essentially from those of earlier workers.<sup>32</sup>

The means which we used to alter pressure in the circulation of the perfused kidney were these: stimulation of the splanchnic nerve; injection of adrenalin; partial occlusion of the renal vein.

Since all of these agencies raised pressure in the renal circulation, and since the conditions of our experiment were such that they could not materially change the blood flow, we seem justified in attributing such results as were obtained to changes in renal blood-pressure.

Each of the three agencies tested increased urine formation in a number of experiments practically without exception.

It will be noted that among these agencies employed is venous obstruction, which in the intact animal always causes diminution of urine, a fact regarded by Heidenhain as the strongest argument

<sup>30</sup> Richards and Drinker: Jour. Pharm. and Exper. Ther., 1915, 7, 467.

<sup>31</sup> Richards and Plant: Ibid., p. 485.

<sup>32</sup> Richards and Plant: Am. Jour. Physiol., 1917, 42, 592.



against filtration. In our experiments, in which it increased urine, there was no stagnation of blood in the glomerular capillaries which might neutralize the effects of increased glomerular pressure as a filtering force. The experiment seems to me to remove the force of Heidenhain's objection and to confirm the suggestion that in the intact animal partial occlusion of the renal vein so lessens the rapidity of renewal of blood in contact with the glomerular endothelium that the effect of increased filtering forces is nullified.

*III. Regulation of Glomerular Pressure.*—The experiments just described have served us in three ways: they yield evidence that rise of pressure alone in the renal circulation can cause increase in urine; they point to a solution of Heidenhain's difficulty which is consistent with the filtration theory; and they provide a point of departure for an analysis of the effects of increased renal pressure. In this last connection the action of adrenalin has been most useful.

If the vascular reaction of a perfused kidney to minute doses of adrenalin is compared with the same reaction of another structure similarly perfused—*e. g.*, the leg—a striking difference appears. Any dosage of adrenalin which causes constriction of the vessels of the leg also causes diminution in volume of the leg, as shown by the oncometer. When a perfused kidney is similarly tested it is found that large dosage of adrenalin causes a similar effect, *i. e.*, constriction of vessels as shown by rise of perfusion pressure and shrinkage of volume of the kidney; but smaller doses, which still cause some degree of constriction of vessels, as shown by the perfusion pressure, cause either no change in or distinct swelling of kidney volume.

In this experiment with the kidney we have an apparent paradox of coincident constriction of vessels, as shown by rise of perfusion pressure, and dilatation of vessels, as shown by swelling of the kidney.

The only reasonable explanation of this paradox which has occurred to us is this: between the afferent and efferent vessels of the glomerulus is interpolated the distensible capillary area of the glomerular tuft. The walls of the afferent and efferent vessels both contain smooth muscle; both are supplied with nerve fibrils (presumably sympathetic), ending in contact with the muscle cells.<sup>33</sup> If under the conditions of our experiment the efferent vessel were constricted a passive rise of pressure must occur in the glomerular capillaries proximal to it, and the distention of these, thus brought about, might cause swelling of the kidney. In support of this view we recall the generalization which Elliott's work has established, namely, that the action of adrenalin is equivalent to stimulation of sympathetic innervation: and we have an observation of our own, made with the frog's kidney, which shows unmistakably that adrenalin has the power of constricting bloodvessels peripheral to the glomerulus.

<sup>33</sup> Smirnow: Anat. Anzeiger, 1901, 19, 347.

In the minds of many physiologists a certain stigma appears to attach to perfusion experiments with isolated organs when the attempt is made to apply results so obtained to the interpretation of events within the intact animal body. If it were possible to demonstrate constriction of the efferent vessel by adrenalin in the intact animal with associated diuresis the force and usefulness of the experiments just cited would be increased. Reason for thinking that this might be possible seemed to exist. The efferent vessel of the glomerulus is a narrower tube than the afferent vessel. A constrictor influence, acting alike on both, would therefore produce a greater increase in frictional resistance to blood flow in the smaller (efferent) vessel; for this reason it seemed probable that very minute amounts of constrictor substances might, by more effective constriction of the efferent vessel, produce simultaneously three effects in the intact animal: diminution in blood flow through the kidney by constriction of efferent vessel; increase in urine by increased glomerular pressure; swelling of the kidney by distention of the glomerular capillaries. The event showed that this combination could be demonstrated following minute, but clearly constrictor, doses of adrenalin and pituitrin.

These experiments seem to me to yield evidence not only that the glomerular process is filtration but also that intraglomerular pressure—filtration pressure—is regulated by the relative degree of constriction or dilatation of the afferent and efferent vessels. This latter belief is intimated in a statement by Ludwig<sup>34</sup> in 1856:

“Since the afferent and efferent vessels of the glomerulus, as well as the roots of the renal vein, contain muscle within their walls, the possibility exists that the blood stream in the kidney changes according to the contractions of these muscles, even though the movements of the heart and the general circulation in the organism remain unchanged.”

In connection with the action of constrictor substances, like adrenalin and pituitrin, it becomes apparent how it is possible for the same substances in different dosage to produce opposite effects. Minute amounts causing more effective constriction of the smaller efferent vessel may increase urine by increasing intraglomerular pressure; larger amounts, by constricting both afferent and efferent vessels, may diminish urine by decreasing ingress to the glomerulus and so lessening both intraglomerular pressure and velocity of flow. The literature shows that small dosage of adrenalin may cause diuresis. Nothing is easier to determine than that larger doses cause partial or complete suppression of urine. Similar apparently contradictory evidence concerning pituitrin can be found.

Permit me now to revert to Brodie's statement of a group of occurrences which he regarded as completely inconsistent with the

<sup>34</sup> *Lehrbuch der Physiologie des Menschen*, 1856, 11, 257.

filtration theory: diminished blood flow through the kidney, increase of kidney volume and increase in urine. This group of occurrences, as we think our experiments indicate, is precisely that which would be expected as a result of preferential slight constriction of the efferent vessel, and instead of being inconsistent with the filtration theory is demanded by it.

From this reasoning it would seem as though any substance which is constrictor to renal vessels should, in suitable high dilution, show evidence of diuretic power unless it lowers general blood-pressure or diminishes permeability of the glomerular membranes. This supposition is now being tested.

I am inclined also to suggest another generalization, based upon this evidence that intraglomerular pressure may be altered by more effective action of a substance upon the efferent than upon the afferent vessel. It concerns the action of arterial dilator substances in general. If it be agreed that glomerular urine is a protein-free filtrate from blood, then it follows that any substance in solution in the blood which causes dilatation of renal arterioles, and which in part passes out of the blood with the glomerular filtrate, must from these facts be potentially diuretic; for its effective concentration will be greater in the blood in the afferent vessel than in the blood in the efferent vessel; and its dilator action will be greater on the afferent than on the efferent vessel, and for this reason alone intraglomerular pressure must rise.

It should be noted that by effective concentration I mean concentration in relation to the colloids of the blood.

Without having the direct evidence to support this idea, I venture to present it in the belief that it is applicable to the glomerular behavior of a large number of substances—water, urea, the caffeine series, salts, etc., all of which are vasodilator, and all of which, we believe, leave the blood stream as it passes through the glomerulus.

If we regard the renal arterioles as very sensitive both to constrictor and dilator substances, as they most certainly are, and if we admit the possibility of such preferential action as I have indicated on either efferent or afferent vessel, we must see in this a very delicate mechanism whereby intraglomerular pressure, and hence the first formation of urine is regulated in accordance with the chemical composition of the blood.

*IV. Description of Glomerular Circulation.*—In this description of experiments, both of our own and of others which concern the nature of glomerular function and its mode of regulation, an implication has been permitted which now appears to me to require correction. Its correction does not, I think, materially alter the force of the conclusions which have just been drawn, but it adds an element in the conception of glomerular regulation which may be of greater importance.

The kidney contains a great number of urine-forming units. The

number of glomeruli in the cat's kidney has been estimated at 16,000; in the kidney of a dog weighing 11 kilos, 150,000; in the human kidney, 2,000,000.<sup>35</sup> For each glomerulus there is a tubule. It seems to me that it has been tacitly assumed in the great bulk of writing on kidney function that the circulation through all of these units is at least roughly uniform—that they take equal part in the sum of activities which made up the total function of the whole organ. I have found one explicit statement of another conception: In Hermann's first work (1859) on kidney function he noted that the two kidneys may eliminate different amounts of urine, and he stated that it was simplest to assume that all parts of the kidney do not act to the same degree all of the time—that one part of the excreting surface may rest or be active while another part is in reserve.<sup>36</sup>

We have observations which indicate that this is a true conception. In the development of the idea that glomerular pressure may be regulated by the degree of constriction of its efferent as compared with its afferent vessel, it became highly desirable that we get evidence as direct as possible concerning changes in size of the glomerulus during the action of adrenalin under controlled conditions of blood flow. In 1919 Krogh, of Copenhagen, published his extremely important paper on the behavior of capillaries in muscle.<sup>37</sup> He used methods of direct microscopical observation of muscles illuminated either by transmitted or reflected light. It occurred to us that the use of the same method might enable us to see the glomeruli of the kidney in operation, provided we could find a kidney sufficiently translucent to permit a certain penetration of light rays. In September of 1920 Dr. Schmidt and I found that the frog's kidney fulfills this demand. When we focused the light of an arc lamp or a 1000 watt "Mazda" lamp upon the ventral surface of an exposed frog's kidney *in situ*, the low power of the microscope showed in the interstices of the radicals of the renal veins nests of capillaries which to our view and that of competent microscopists could be nothing else than glomerular tufts. It soon became possible to distinguish the outline of the capsule, in many cases the entrance of the afferent vessel, and in not a few instances the exit of the efferent vessel as well. Because not all of these structures had the same appearance and to prevent an egregious error, we spent some time in attempts to identify a certain group of glomeruli in the living kidney, to follow this group through processes of fixation and embedding in order to prepare a stained section which should contain the structures examined in the living kidney. With the aid of Dr. B. Lucke this was successfully done. This identifica-

<sup>35</sup> Cited from Cushny: *The Secretion of Urine*, p. 5.

<sup>36</sup> *Sitzungsberichte d. k. Akad. d. Wiss. zu Wien, Math.-Naturwiss. Cl.*, 1859, 36, 349.

<sup>37</sup> *Jour. Physiol.*, 1919, 52, 409.

tion has given a sense of security concerning previous and subsequent observations which we might not otherwise have had.

When the lateral border of the ventral surface of the frog's kidney is observed in this way, the large renal veins and their tributaries are most prominent. Arterial branchings and the divisions of the renal portal vein, being deeper in the kidney, are less obvious. Details of the tubules are commonly indistinct. In the interstices of the veins are seen the glomerular tufts. They vary in size from 80 to 250 microns in diameter. Some show a great multiplicity of tortuous narrow channels, each of a diameter sufficient to permit passage of one red cell. The capillary wall is not easily seen. The blood flow through these channels is oftentimes bewilderingly rapid. In other instances the appearance is of another type: instead of a multiplicity of channels only one or two capillary loops are visible; these have wider diameter and show sluggish flow of more densely packed corpuscles. In the more slowly flowing blood streams pulsations are apparent; in the more rapidly flowing stream it may not be. Between these two extremes intermediate variations occur.

Concerning the problem which was the impetus for beginning these observations—*i. e.*, the question whether the glomeruli could be seen to swell as a result of the constrictor action of minute amounts of adrenalin upon the efferent vessel—the answer is still indeterminate. A series of measurements by Dr. Schmidt of glomerular diameters before, during and after the injection of doses of adrenalin of the order of 0.1 cc of 1 to 1,000,000 showed swelling, and in so far were confirmatory of our conclusions drawn from the mammalian experiments. But since a distinct improvement in the general circulation resulted from this injection the increased glomerular size may have been due to this. Before a final answer can be obtained the experiment must be performed on the kidney, perfused with blood at a constant rate. This experiment has not yet been made. Other features of the glomerular circulation seemed to demand more immediate study.

In our earliest experiments the variability of our preparations was striking. In some preparations as many as eight glomeruli could be counted in a field of 2 mm. diameter; in others only three or four in the whole kidney, in so far as it was accessible to inspection. Our frogs were pithed, and if two or three drops of blood were lost in this operation the number of glomeruli to be found in the kidney was small. If, however, such a frog were immersed in a saline bath, or if his abdominal cavity were filled with isotonic salt solution, the number of visibly active glomeruli increased.

Acting on the suggestion which this fact afforded, we have made a series of counts of the glomeruli which show active circulation under varied conditions.

Bits of silk thread were laid transversely across the surface of the kidney at approximately equal distances of about 2 mm.

(the diameter of our low-power field). From five to eight fields were thus separated for ease in counting. A bit of cover-slip was lightly laid over these, both to prevent displacement of threads and to avoid surface glare.

I shall cite figures to show alterations in the number of glomeruli in which blood was flowing before, during and after the introduction of various substances to be mentioned.

1. *Isotonic Salt Solution*.—As has been mentioned, salt solution is absorbed from the open abdominal cavity of the frog, and as a result circulation improves if it has been lessened from hemorrhage. These figures illustrate: Soon after preparation five fields showed 5 active, 8 inactive, total 13 glomeruli. Thirty minutes after salt solution had been introduced into the belly the same fields showed 28 active, 0 inactive, total 28 glomeruli. (By "active" glomeruli we mean those showing active circulation.)

2. *Injection of Blood*.—0.5 cc of whole blood was taken from the aorta of one frog and immediately injected into the anterior abdominal vein of a frog, whose glomeruli had been counted. Before injection, active glomeruli 10, inactive 27, total 37; five minutes after injection, active glomeruli 39, inactive 9, total 48.

3. *Injection of Isotonic Salt Solution*.—0.5 cc of 0.6 per cent. Before, 41 active, 9 inactive, total 50; ten minutes later, 54 active, 8 inactive, total 62; twenty minutes later, 44 active, 6 inactive, total 50.

4. Then *urea* 0.1 cc 20 per cent. After, 65 active, 2 inactive, total 67.

5. *Caffein*, 7 fields counted: Before injection, 81 active, 11 inactive, total 92; 0.1 cc 2 per cent *caffein*, five minutes later, 104 active, 0 inactive, total 104.

6. *Glucose*.—0.1 cc, 10 per cent glucose: Before injection, 31 active, 12 inactive, total 43. Followed by progressive increase in number of active until thirty-five minutes after, 62 active, 3 inactive, total 65.

7. *Hypertonic Sodium Sulphate* (5 per cent): 0.1 cc. Before, 6 active, 0 inactive, total 6; after thirteen minutes, 51 active, 0 inactive, total 51.

8. *Adrenalin* constrictor dose 0.1 cc, 1 to 100,000: 3 fields; before injection, 49 active; immediately after, 12 active; seven minutes later, 48 active.

9. *Pituitrin*: Constrictor dose, 0.1 cc 1 to 10 dilution of pituitrin "S." Before, 14 active, 5 inactive, total 19; after, 0 active, 16 inactive, total 16; later, 5 active, 12 inactive, total 17.

These and many similar observations have led to the conclusion that even under the most favorable of operative conditions, *i. e.*, with the least loss of blood, all the glomeruli of the kidney of the frog do not receive blood simultaneously. Conditions which depress the circulation, such as blood loss or destruction of the cord, or

agencies which constrict bloodvessels in the kidney, such as constrictor doses of adrenalin or pituitrin, lessen the number of glomeruli which receive blood. Plethora, absorption or injection of isotonic salt solution, hypertonic NaCl, hypertonic sodium sulphate, urea, glucose and caffein—all are capable of impressively increasing the number of glomeruli which receive blood at one time.

Not only is the number of glomeruli showing active circulation altered by the agencies which I have mentioned, but also the number of capillary loops within a single glomerulus which take part in the capillary blood flow. Earlier in this section I referred to glomeruli of two rather widely different aspects in so far as blood flow through them is concerned; one in which narrow rapidly flowing currents of blood indicate a complex network of tortuous channels; others in which one or two loops only are visibly filled with blood and in these blood usually flows more slowly and in a wider stream. The dilator agencies, urea, caffein, etc., mentioned above have the power of transforming a glomerulus of the latter type into one of the former.

Adrenalin, on the other hand, in constrictor dosage transforms a glomerulus showing a multiplicity of channels with rapid flow into one with fewer patent capillary loops and slow flow.

This indicates that just as all glomeruli in a kidney do not receive blood at once, so too in a single glomerulus not all the capillary loops need be patent at one time. Dilator (diuretic) agencies increase the number of capillaries in the glomerulus through which blood is flowing; constrictor substances and depression of the general circulation lessen the number.

Another characteristic of glomerular blood flow in the frog's kidney is that it is not always continuous but may be intermittent. Intermittence of glomerular flow is more liable to occur in a kidney showing active rapid circulation than in one in which blood flow is more sluggish. It was first observed by us in frogs after improvement of the circulation following absorption of salt solution; it has, however, been observed in frogs subjected to no other preparation than that required for looking at the kidney. The intermittence of blood flow may be of different types; in some instances there may be diminution in all and cessation in many at the same time, as though resulting from an influence outside of the kidney, as, for example, by changes in the general circulation or as a result of nervous stimuli to the bloodvessels. This type is easily understandable.

What we think of, however, as true intermittence is less easy to comprehend: two adjacent glomeruli may be situated within a few microns of each other; blood flow in one may stop completely, to be resumed after an interval, without interruption or even perceptible alteration in flow in the other. This phenomenon may be multiplied so that in a favorable field one sees a lively series of irregular interruptions in flow through the various glomeruli visible.

The interruptions bear no relation to the heart-beat. The intermittence of one glomerulus was timed with a stop-watch—15 seconds on; 12 seconds off; 27 seconds on; 11 seconds off.

In another, 103 seconds on; 10 seconds off; 90 seconds on; 45 seconds off.

In another preparation, 5 glomeruli were watched at once: Nos. 3, 4 and 5 stopped at the same time; Nos. 1 and 2 kept on actively. After three minutes No. 4 begins; Nos. 3 and 5 are blank.

We have tried to get a graphic representation of this phenomenon. A keyboard with five keys was connected each with a signal magnet arranged to write on a drum. Five glomeruli in a field were chosen and a key assigned to each. Discontinuance of flow was registered by pressing the key and keeping down until the flow resumed. The recorder also noted on the drum obvious variations in rapidity of flow which could not be designated as complete cessation or resumption. Charts were then made of these records.

Study of these charts forced the conclusion that while at times there are interruptions common to all, in the main the circulatory activity of one is independent of others; and the inference is drawn that a local regulatory mechanism must exist analogous to that shown by Krogh to exist in muscles.

Preliminary attempts to gain deeper insight into the circumstances of this phenomenon have been made. Not very much can safely be stated at present. We are sure that the phenomenon of intermittence persists after complete destruction of the whole central nervous system—brain and cord. There is evidence that intermittence of the glomerular circulation is commonly associated with simultaneous and synchronous intermittence of the afferent vessel. In this connection it is very striking that when flow stops abruptly in a single active glomerulus, corpuscles do not remain stagnant in its capillaries; they may remain for an instant, then they fade out of view and the whole glomerulus may become invisible. This must mean that the capillaries of the glomerulus possess power of independent contraction capable of emptying their lumina after blood has ceased to flow. This statement must be held as applicable to the afferent and efferent vessels, since they as well as the glomeruli are emptied when blood flow stops. Dr. Schmidt has made one observation which we hope to repeat: In one instance capillary flow in the glomerulus ceased abruptly and blood cells disappeared from it; but the afferent vessel remained full of blood, the corpuscles oscillating back and forth at the entrance of the glomerulus until presently the glomerular capillaries opened and flow through the whole structure resumed.

This emptying of the capillaries after cessation of flow—indicating, as we believe, independence of contractility of their walls—is much less marked or may be absent in the dilated sluggishly flowing capillaries of some of the glomeruli to which reference has been



made. These are likely to remain engorged with cells when the flow ceases. We take this to mean that there are normal differences in tonus and normal variations in tonus.

We do not yet know what the nature of the influence which regulate this tonus is.

Making the assumption that these observations are applicable to the mammalian kidney, they give us a conception of glomerular circulation different from that which I had previously held. Instead of a uniform circulation of blood through all the glomeruli, varying with general and renal blood-pressure, we conceive of a circulation, restricted under conditions of moderate blood flow to only a fraction of the glomeruli; and instead of equal circulation through all of the capillaries of a single glomerulus, we conceive of the possibility of restriction of flow through a fraction of the available pathway. This restriction in number of functioning glomeruli and in patent capillary loops may be brought about by general influences (circulatory and nervous) brought to bear from outside the kidney and unequally effective in different units of the kidney through anatomical differences, such as length of vessel; in addition we think of the restriction as due to a local, peripheral control of contractile power, not only of afferent and efferent vessels, but of the intervening capillaries as well. The phenomenon of intermittence permits us to think of alternating rest and activity of glomerular structures and prevention of damage such as would conceivably result from prolonged interruption of blood flow.

The phrases "dilatation of the kidney vessels" and "constriction of the kidney vessels" come to mean not only the increase and decrease in volume and rate of a stream already flowing, but also the increase and decrease in actual number of functioning glomeruli and of open glomerular capillaries. The possibilities in the direction of increase or restriction of filtering surface become more impressive.

On this basis it is not difficult to understand how relatively enormous changes can take place in glomerular blood flow without correspondingly great changes in the size of the kidney as registered by the oncometer, for obviously the capsule does not collapse when flow through the tuft ceases. It is easy to understand and to accept such puzzling experiments as those of Loewi—in which the ability of blood flow to increase under the influence of caffeine in a kidney embedded in plaster of Paris was demonstrated.

It becomes easier to understand how a kidney might eliminate from blood of the same composition and in equal spaces of time urine of widely different composition, for a urine issuing as the result of highly active blood flow and high glomerular pressure in a smaller number of glomeruli must be different from that which issues as the result of slower blood flow and lower glomerular pressure from a larger number of glomeruli. The resorptive powers of the tubules would be effective to different degrees.

The difficulty of injecting the glomeruli *uniformly* even in fresh kidneys is comprehensible, as is also the lack of uniformity among the glomeruli in the action of circulating toxic substances.

A lead may be given concerning the causation of albuminuria under conditions not far removed from the physiological; it is a very old observation that complete arterial interruption of the circulation in the kidney for a short time is followed by albuminuria. If intermittence of glomerular flow is a normal phenomenon it would appear that albuminuria might occur if for any reason the duration of the normal intermittent cessation of flow increased.

I will give the briefest résumé of the chief points presented:

1. New evidence has been secured that increment of blood-pressure, uncomplicated by increment in velocity or volume of blood flow in the kidney, increases urine formation. This is regarded as added support of the filtration hypothesis.

2. Evidence has been secured indicating that some of the most weighty objections to the filtration hypothesis can be reasonably explained in a manner consistent with it.

3. Indications have been shown that nervous stimuli and chemical substances may exert different degrees of effective influence upon the afferent and efferent vessels of the glomerulus and that this may be a factor in that automatic regulatory control of glomerular filtration which is responsible in part for the maintenance of constancy of blood composition.

4. And, finally, a new description of the mode of circulation through the glomerular vessels has been presented which, when verified and extended, we hope will be of service in the study of the normal and pathological physiology of the kidney.

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## A FURTHER STUDY OF THE QUANTITATIVE VARIATIONS IN THE VIBRATION SENSATION.<sup>1</sup>

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THE first contribution to the study of the vibration sensation was made by Rumpf<sup>2</sup> in 1889. A steel tuning-fork was used, and the handle was so made that it was suitable for application of it to the skin surface after the vibration was started. Forks of different rate of vibration were used in this study, as it was found that in different parts of the body different rates of vibration were

<sup>1</sup> Read before the Association of American Physicians, May 11, 1921.

<sup>2</sup> Neurol. Centralbl., 1889, 8, 185.

better appreciated. Rumpf regarded the procedure merely as a means for the more careful study of skin sensation.

In 1897 Treitel,<sup>3</sup> unaware of Rumpf's work, experimented with a tuning-fork of 128 vibrations, with which the variations in the length of time of the perception of the sensation were studied. He discovered the important fact that under certain pathological conditions tactile sensation and vibration sensation bear a different relation to each other and the one may be altered without alteration of the other. Contrary to the conclusion of Rumpf he decided that the vibration sensation is to be distinguished from a sense of pressure and a sense of touch.

Max Egger is usually regarded as the first to study the vibration sensation. Certainly, he was the first to demonstrate the feasibility of testing the sensibility of bones by means of a tuning-fork. The idea was suggested by the extreme sensitiveness of periosteal lesions. By lifting up a fold of skin in a thin subject and placing it between a vibrating tuning-fork and a fixed object only the very slightest vibration was detected. When the skin was allowed to fall back into place and the instrument was applied it was found that the appreciation was increased tenfold.

Egger<sup>4</sup> demonstrated that this perception of vibration sensation was entirely independent of the presence or absence of cutaneous sensibility. More recently Goldscheider showed that Egger was in error in his conclusion that the vibration sensation is perceived only through bone. He found that the soft parts are susceptible, though not to so marked a degree, owing to the physical property of the tissue. Goldscheider<sup>5</sup> further thought that the observation was dependent in part on the condition of cutaneous sensibility. He experimented with anesthetization of the skin. To test the cutaneous sensibility the instrument was very lightly applied to the skin surface, and to test vibration it was applied much more firmly through the compressed skin. He did not regard it as a specific sensation but as an expression of the sensation of rhythmic interrupted irritation of the nerves that are responsible for the sensation of contact or pressure.

Bing is quite emphatic in stating that through cocain anesthesia tactile, pain and temperature sense may be abolished while the vibration sensation is preserved, and, further, that it is usually not noticeably decreased. He shows many good grounds for the sharp separation of tactile and vibration sensation.

L. F. Barker<sup>6</sup> is disposed to regard the sensation of vibration as due to the result of the stimulation of the touch points in the skin.

<sup>3</sup> Arch. f. Psychiat., 1897, 29.

<sup>4</sup> Jour. de physiol. et de path. gén., 1899, No. 3, 1. Rev. neurol., Paris, 1908, 16, 345-351. Comptes rendus de la soc. de biol., 27 Mai, 1899, p. 423. Comptes rendus de la soc. de neurol., 4 Febr., 1901.

<sup>5</sup> Berl. klin. Wchnschr., 1904, No. 14.

<sup>6</sup> Monographic Medicine, vol. 4, p. 136.

He says that though this sensation may disappear before there is complete tactile anesthesia, still it seems to indicate that among the earlier disturbances of tactile sensation must be counted an inability to perceive successive impulses of short duration as separate sensations.

In 1903 Rydel and Seiffer<sup>7</sup> gave to the vibration sensation the name *pallesthesia*, which was a step in the direction of separating it as a different sensation from tactile and other sensations.

For clinical purposes Bing preferred to use the Gradenigo vibrator. A clear description of this instrument is not available. It seems to depend on an optical device as the means of determining a point of fixed amplitude. Barker preferred the C fork of 128 vibrations provided with a Gradenigo triangle on one prong, which permits, he says, of the application of vibrations of very different numbers and the number at the instant of vibration disappearance may be exactly recorded. During the progress of this work various instruments with the Gradenigo triangle were used, but the results did not seem to justify a continuance because of the difficulty in general standardization. It seems justifiable to recall to the reader that a tuning-fork can only vibrate at a fixed rate regardless of the violence of the starting blow. The only thing the blow can alter according to its degree is the amplitude of the vibration or the "degree of swing." To reach some means whereby the amplitude can be standardized is ever the difficulty in perfecting an instrument for quantitative work.

R. T. Williamson,<sup>8</sup> the English pioneer in the study of the vibration sensation in neurology, mentions in his writings the advantages of the Gradenigo instrument. He was impressed with the fact that by it sensation in different parts of the body can be accurately measured. Williamson worked with a C<sup>1</sup> fork nine inches long with prongs five and a half inches long.

In 1911 J. L. M. Symns,<sup>9</sup> working in Guy's Hospital, adopted a tuning-fork for quantitative work which made possible the exact charting in numerical ratio of the responses of the subject in different points on the body surface. The instrument of Symns has a small "window" placed between the prongs at the free ends. If the amplitude is wide enough the prongs separate sufficiently to allow to be seen the two little slots which differ slightly in depth. As soon as the vibration dies out sufficiently the window or slot is covered up. Unless the vibration is quite active the window will not appear. The observer strikes the instrument and then holds it up between his eye and a bright light, preferably a window, and

<sup>7</sup> Arch. f. Psychiat., Berlin, 1903, 37, 488-536. Neurol. Centralbl., 1903, No. 7. Berl. Ges. f. Psych. u. Nervenkr., 9 Marz, 1903.

<sup>8</sup> British Med. Jour., July 20, 1907.

<sup>9</sup> British Med. Jour., 1912, 1, 539. Guy's Hospital Reports, 1912, 66, 120. Quarterly Jour. Med., 1917, 2, 33-58.

continues to watch the gradually lessening light which is allowed to pass through the slot. At the instant when no more light can be detected the handle of the instrument is applied to the bony point under consideration and the subject told to note the vibration carefully, and at the instant when the vibration is no longer detected to give a suitable signal. The time during which the sensation is felt is recorded in seconds. Symns used a stop-watch, but it is not essential and has the disadvantage of requiring an assistant.

The present work<sup>10</sup> was planned to serve as a continuance of the observations begun by Symns in the same clinic in 1911. Dr. Hurst and Dr. Symns were of the opinion that the normal range established by the latter had been based on too small a number of cases. One hundred normal individuals were studied by me in making a graph of the normal variations. The subjects were bed patients suffering from no nervous disease, willing to coöperate in the test and mentally intelligent. The graph constructed on this series of normal observations varied markedly from that constructed by Symns on a fewer number of observations. This was found to be due to the difference in the two instruments used. Through the help of Mr. H. G. Drew, of Messrs. Down Brothers, Ltd., of London, the makers of the instrument, it was soon learned that while the instrument used in the present work and that used by Symns were both of 108.5 double vibrations per second, and with identical windows the sources of difference could be readily accounted for and in large measure eliminated in future manufacture. Variations in weight and temper of the shaft caused a variation in vibration appreciation. A vibration of 2 mm. swing at the fork end is differently transmitted at the handle end if the rigidity of the fork varies. The instrument used in this work has been carefully weighed and measured by the manufacturer and made the standard. The window, which is really a double slot, has been carefully registered and every precaution will be taken to manufacture instruments conforming to it. It must be remembered, however, that a hand-wrought instrument can never be exactly duplicated, and it is not possible to exactly reproduce temper. It was thought desirable to standardize the instruments in such a way that a normal graph might be supplied with each instrument to facilitate the exact recording of the curve in each individual case.

In the diagrams it will be noted that the observations are made on various bony points of the body and recorded in seconds. The investigation is done in many other ways by a large number of observers. Dr. Henry Head does not use a windowed instrument and does not select the bony points used in the present work. One important part of his examination is timing the period during

<sup>10</sup> Guy's Hospital Reports, January, 1921.

which the vibration can be detected on one side after the vibration can no longer be detected on the other side. That is, he holds the vibrator in contact with a part on the right side until the vibration cannot be felt, then quickly transfers the instrument to the other symmetrical part on the left side and notes the time in which the lessening vibration can be felt. The procedure is then reversed. Dr. Gordon Holmes uses a simple heavy tuning-fork without window and does not make time observations with standardized amplitude. His conclusions are based more on qualitative returns than on quantitative.

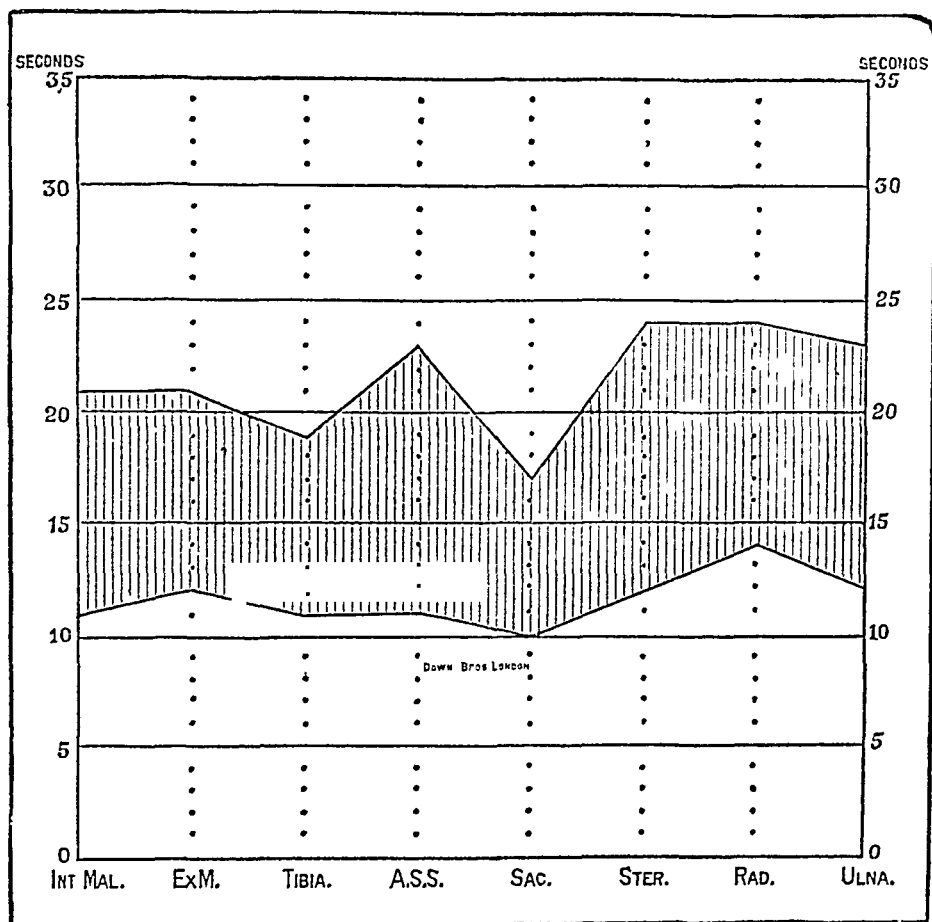


FIG. 1.—Normal range established in 100 non-neurological cases.

It was thought by those interested that the standardization of an instrument with a standard normal range, as has been attempted in this work, might open the way for numerous observations by many observers, resulting in the accumulation of data which is much needed before final acceptance of many of the claims to be made can be expected.

The justification for this present work is the fact that until quantitative variations are appreciated the value of the test is lost

at a time when its aid is most needed. Before total loss of vibration appreciation occurs there is a gradual dimming which with this instrument can be exactly recorded day by day and the progress of the process noted. For example, in *tabes dorsalis* there occurs late in the disease frequently an entire loss of vibration appreciation in the lower half of the body; but, on the other hand, early in *tabes* before other signs of recognized value appear it will be found that there is a definite quantitative diminution of the time during which these vibrations of standard amplitude are felt.

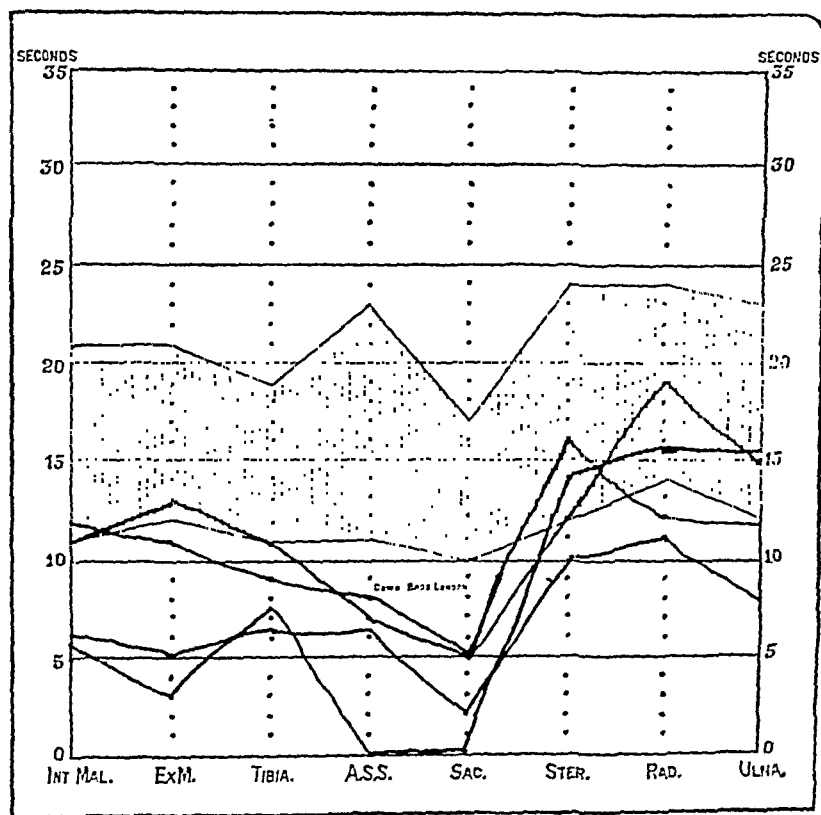


FIG. 2.—Vibration response in 4 cases of tabes.

It is beyond the scope of this article to enter into a discussion of the nature of the vibration sensation and its relation to other sensations. Suffice it to say that under certain pathological conditions of the nervous system there is definite departure from the normal.

The most notable variation of a fixed sort was seen in *tabes*, as has been mentioned. Eighty cases were studied in various stages, and in large part these cases were kept under prolonged observation watching changes which occur much more markedly in vibration

than in any other sensation. In not one of this series was there an exception to the rule that in the lower half of the body there always occurs a reduction in the time of appreciation of vibrations of a fixed amplitude. This reduction in time was singularly constant in its occurrence over the sacrum. It is rare indeed in any case of tabes, however early, to record a time of more than five seconds over this point. In a large proportion of the cases there was no response at all over this portion of the body. In two or three instances the time recorded was as much as six or even seven seconds. Fig. 2 shows the curves of 4 cases of tabes overlaid. The general tendency to dip at the sacrum is well illustrated. In many instances this low response or absence of response occurs when the instrument is applied to the anterior-superior spines of the ilia. It is exceptional for the curve in tabes to fail to fall within the normal range in the upper extremity, and in some instances there is really a high response in this part of the body. This is one of the distinctive differences between tabes and multiple neuritis. In the latter the normal range is seldom encroached on at any point and the "sacral dip" is absent.

This study has led to the conclusion that loss of vibration appreciation is the first sensory loss in tabes. This is illustrated in a man studied in the Addison Ward, Guy's Hospital, whose diagnosis was thoracic aneurysm. The blood in this case was Wassermann negative while the spinal fluid was strongly positive. There were no disturbances of tendon reflexes; the pupils were negative and careful study of skin sensation failed to reveal any areas of analgesia. The curve represented in Fig. 3 shows a low vibration response. It will be noted that the loss is not total but merely a quantitative change which would be readily overlooked were the investigation merely qualitative. This patient was held in the hospital over a long period, and we had the satisfaction before his discharge of seeing the development of areas of analgesia over the tibiae. It seemed justifiable after a study of a number of such cases to conclude that analgesia followed the alteration of vibration response. In many instances the finding of a low vibration response prompted a careful study of the whole body surface, with the result that certain areas of analgesia were sometimes found. In Fig. 4 the patient, whose reflexes were preserved, showed no appreciation of pain when a pin was plunged into the tip of his nose deep enough to hold it in position. Vague gastric cases in which pain was the predominating factor, studied by the vibration test, proved the usefulness of the procedure. In some clinics gastric crisis as a very early symptom of tabes is frequently noted. Why there should be a difference in this observation in different places is not readily understood. In collecting the normal hundred on which the normal range was established gastric cases were sought after because of the non-neurological character. This opened up a most



interesting field, for it was found that in a number of instances these cases showed extraordinary abnormalities in the vibration response. In one case a tentative diagnosis of carcinoma had been made by a very capable house physician. Study of the nervous system showed gastric crisis in early tabes. In another case in the same ward ulcer had been diagnosed and the patient had been on rigid treatment for some time. Vibration study

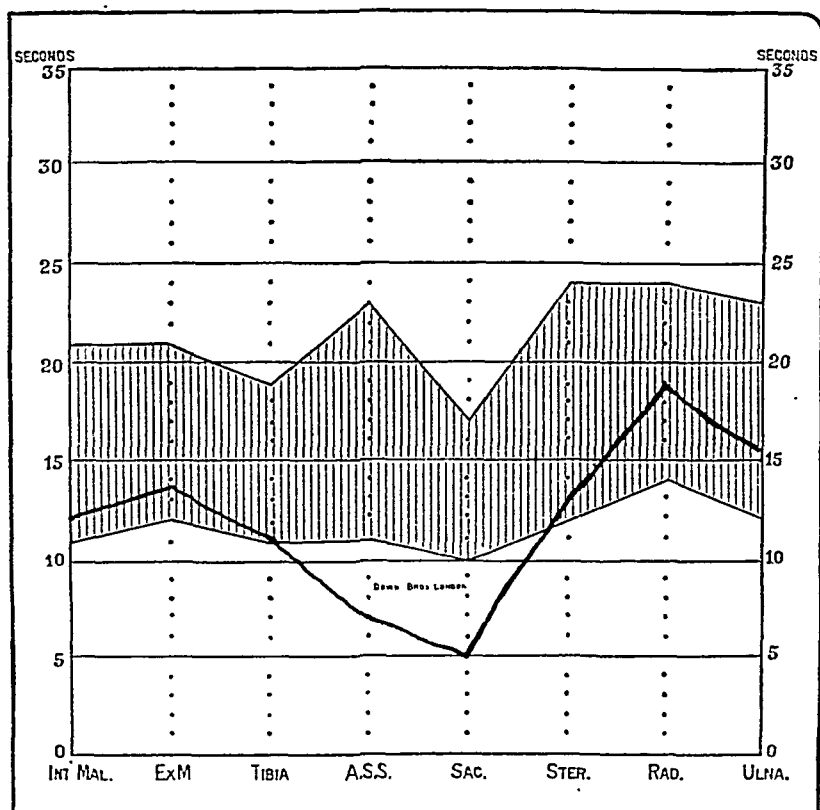


FIG. 3.—Man, aged fifty-five years. Admitted to Guy's hospital (Addison Ward) for aneurysm. The blood was Wassermann negative but the spinal fluid was strongly positive. The vibration curve was that of tabes, and he was kept in the hospital until other signs developed sufficient for a confirmation of this diagnosis. (Guy's Hospital Reports, January 1921).

opened the way for a correction of the diagnosis, which was clearly gastric crisis in early tabes. Recently a case was studied in which the vibration response was distinctly that of tabes. Gastric pain was the symptom, and a most careful chemical and fluoroscopic study had been made. The tendon reflexes were preserved and there was no Argyll Robertson pupil, though the pupils were contracted. Analgesia of the skin of the face as well as other scattered areas suggested tabes, which was verified by spinal puncture. In

still another case now under observation the diagnosis of carcinoma seemed well justified, but vibration suggested tabes, which was borne out by the Wassermann test and cell count of the spinal fluid.

In the 80 cases studied there has not occurred a single instance in which there was not a definite time reduction in vibration response, which usually manifested itself in the form of the "sacral dip." In this other points of the lower half of the body frequently shared. It can be safely stated that any case with no

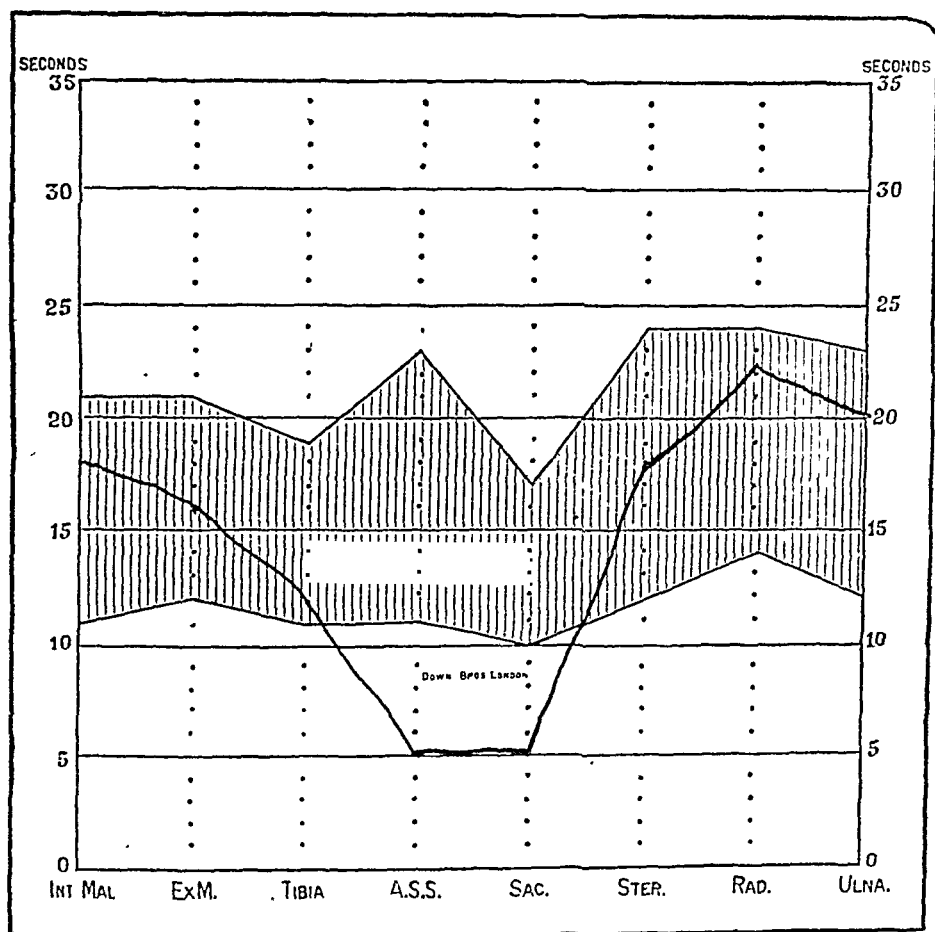


FIG. 4.—Tendon reflexes preserved. Marked analgesia of the skin of the face.

reduction in the time of vibration response over the sacrum is not tabes, an observation which can be easily made in one-half a minute and relied upon without further investigation.

In multiple neuritis there was noted decided reduction in the vibration time. The distinctive "sacral dip or the notch," so marked in tabes, did not occur in any case. There was a general reduction of the time, but a tendency for the sacral point to be relatively high and in many cases higher than the other points. In addition to this there was usually absent that tendency so

marked in tables for the time response of the upper extremity to be normal, making a curve which in that part of the body falls well within the normal range. In diabetes it was interesting to record the improvement in sensation indicated by the vibration curve in those cases receiving proper dietetic treatment. In a case of multiple neuritis occurring in a woman who was a victim of pellagra, seen in the service of Dr. Edwin Bramwell, in the Royal Infirmary, Edinburgh, there was this definite reduction in vibration time with the high point over the sacrum. It was notable in

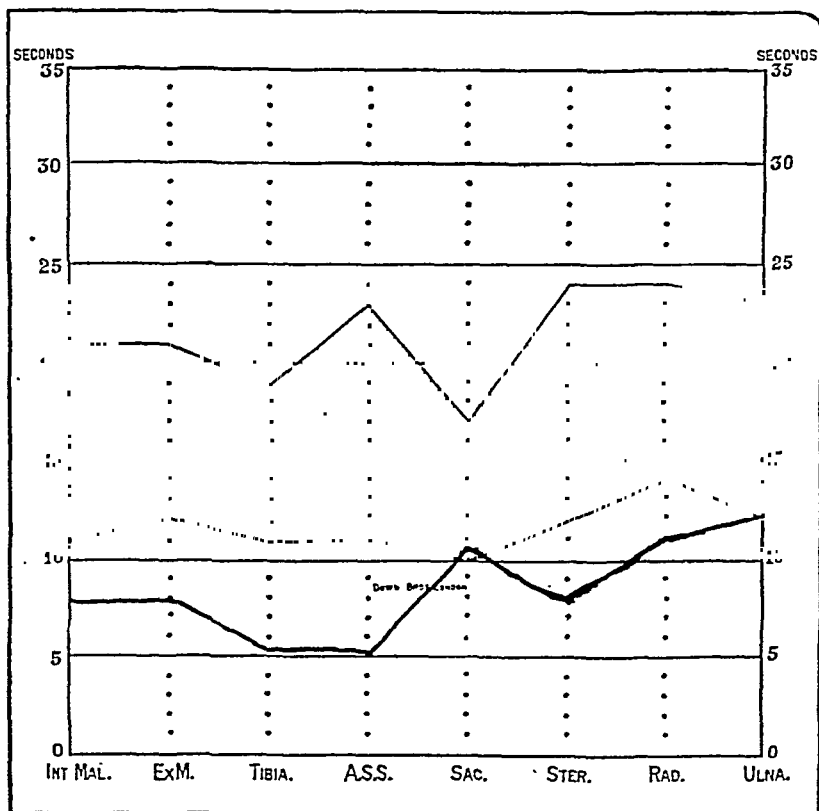


FIG. 5.—Multiple neuritis in pellagra.

this case that pain and tactile sensations were not disturbed and temperature sense only slightly. The vibration time is recorded in Fig. 5.

Three cases of Friedreich's ataxia were studied in Guy's Hospital and showed a loss in the vibration time quite like the changes noted in early tables. The loss of vibratory appreciation was not complete, and would have been overlooked if a qualitative test alone had been made. As in tables there is a "sacral notch" in the curve of these cases.

Subacute combined degeneration of the spinal cord in association with pernicious anemia was studied in 5 cases. In all cases there was a definite loss of the vibration response which, until late in the process, was confined to the lower half of the body, with little abnormality in the upper half. In 1 of these cases the loss was complete in the feet; marked over the tibiae, but not entirely lost; less over the anterior-superior spines and still less over the sacrum, with a gradual ascent in the upper portion of the body. This is seen in Fig. 6, which is made of 2 such cases.

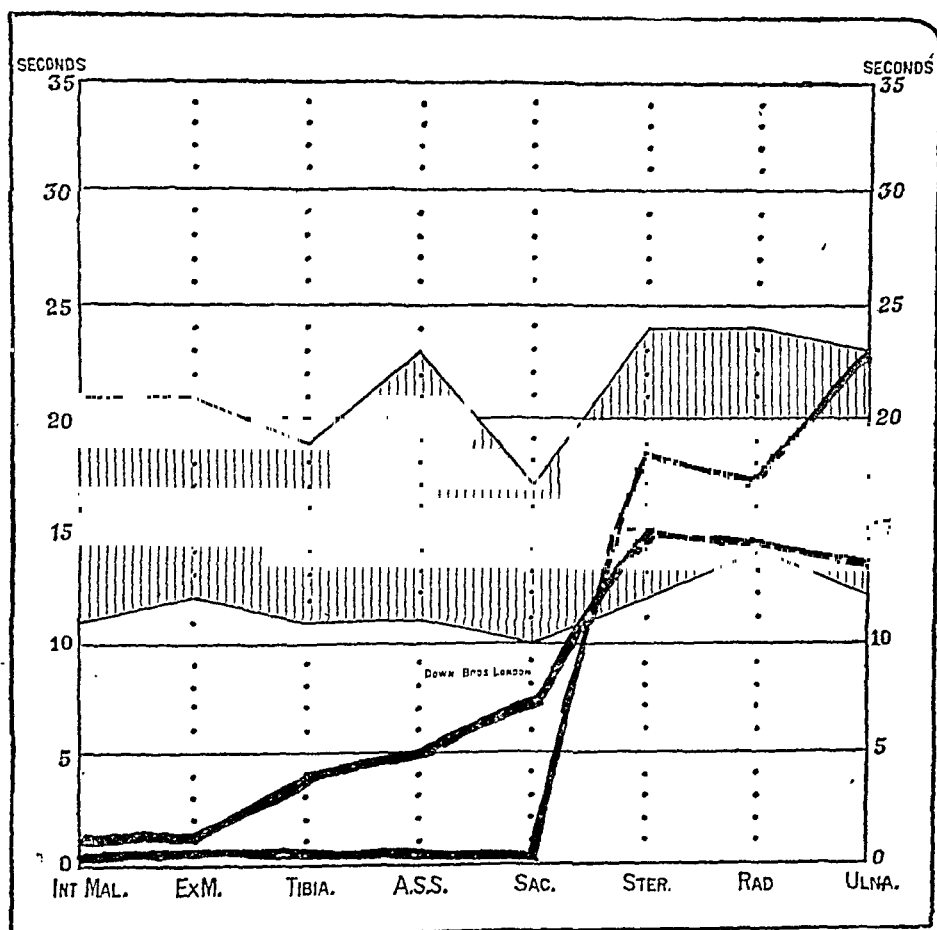


FIG. 6.—Two cases of subacute combined degeneration of the cord in pernicious anemia.

In all of these cases the "sacral notch" of tabes was not pronounced. The curve can be readily distinguished from that of multiple neuritis.

One case studied caused much confusion because the response over the sacrum was entirely absent while the blood and spinal fluid were negative to the Wassermann reaction. Incontinence of bowel and bladder were present. Study of skin sensation about the anus and down the lower limbs gave the characteristic findings of a lesion of the cauda equina.

One of the most fertile fields for the study of the vibration sensation is syphilitic meningomyelitis. In this condition the vibration response was found to be reduced in the lower half of the body, but there was more evidence of asymmetry than is usually noted in such cord lesions as tabes. The great helpfulness of the test seems to be in gauging improvement. It seems probable that an improvement in the spinal fluid will run more or less parallel with an improvement in sensation, and this may be measured in a quantitative way by using the vibration sensation. A beginning only has been made in this work which requires much time and very exact laboratory work by an expert serologist.

In conclusion, I would express my thanks to Dr. A. F. Hurst, of Guy's Hospital, under whom the work was done for aid of every sort; to Dr. Gordon Holmes, for suggestions and clinical opportunities at the National Hospital, Queen Square, at Charing Cross Hospital and at Moorfields; to Dr. Edwin Bramwell, for material and much aid at the Royal Infirmary, Edinburgh; to Sir James Mackenzie, for an opportunity to do further work at the Clinical Institute of St. Andrews, Scotland.

## PERIPHERAL AND RADICULAR TYPES OF EPIDEMIC ENCEPHALITIS.<sup>1</sup>

BY FOSTER KENNEDY, M.D.,

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It is only for the purpose of presentation of different clinical aspects of epidemic encephalitis by different observers that we have in this conference divided with some arbitrariness the disease into different clinical groups. A clinical discussion under these circumstances therefore must begin by a disclaimer that the type assigned to each author is ever a disease of its own genus, and by an assertion that it merely represents a variety in which the virus has fallen with some greater incidence on one part of the body than on another. Of the circumstances which go to permit this variety of form we know little: naturally, disease pictures will vary with the structure affected and variety in such pictures following nervous lesions is furthered because from lesions of the nervous system we may have either obliteration of normal function or release of functions normally controlled by centers higher in the neural hierarchy.

It is probable that variety of clinical form in epidemic encephalitis is also often produced by variety of virus or by a constant virus

<sup>1</sup> Read before the Association for Research in Nervous and Mental Diseases, December 29, 1920.

varied by appearing in different evolutionary guises. However this may be it is certain that the peripheral nerves and spinal roots are affected in encephalitis to a considerable degree. Abrahamson says that in 60 per cent of his cases unmistakable signs of radiculitis were present. This is a higher figure than has been obtained in our series at Bellevue Hospital; we have been slow, however, to ascribe to root or peripheral infection subjective symptoms unsupported by objective phenomena; nevertheless, in some cases the distribution and character of the pains have forced us to the same conclusion; in a few others, sensory changes similar to those found in *tabes dorsalis* have been present; in a small number there have been localized atrophies of muscles such as would occur from involvement of contiguous anterior roots. Palsies of single cranial nerves are not uncommon, the seventh and third nerves being those most usually affected. It should be pointed out that the involvement of the seventh nerve in most of our cases has not been accompanied by any defect either of the fifth, eighth or sixth nerves, a consideration which would exclude the possibility of the lesion being in the pontocerebellar angle or in the nucleus of the facial nerve in the pons, and would compel observers to explain the facial palsies in these cases by a lesion of the seventh nerve in its parenchyma. Not only were single cranial nerves picked out for damage by the infection, but occasionally single peripheral nerve trunks were involved in similar fashion. An interesting example of this was seen in a riveter who in April, 1920, began suddenly to have sharp lancinating pains in the arms and shoulders accompanied by much weakness in the upper extremities. When examined, some three weeks after the beginning of these symptoms, he was found to have a noticeable loss of power in both serratus magnus muscles, the right scapula being winged on raising the arm on that side. The patient had diplopia, heavy sweating, slowness of emotional initiative and a mask-like facies some four weeks after the development of his peripheral nerve symptoms. It is at least an interesting speculation whether this man's occupation as a riveter, imposing reiterated violent exertion of his serrati and notably of the right muscle, could have had any determining effect on the incidence of the disease on the long thoracic nerve.

Several observers, notably Pardee and Barker, have described cases of severe girdling pains beginning in the cervical region, with persistent hiccough and descending to the lumbar region and lower extremities. None of their cases had any objective sensory losses, but all had a pleocytosis in the spinal fluid. It is remarkable that more such patients had not herpetic manifestations; only one of the Bellevue group had herpes, and that was confined to the left auricle and external auditory canal, and was associated with a complete left facial palsy of a peripheral type; a geniculate ganglionitis was in this case the presumptive lesion.

The prognosis in the peripheral and radicular varieties of this disease is good, a happy situation which unhappily prevents pathological confirmation of clinical diagnosis. However, in cases fatal through cerebral involvement there have been found in the posterior root ganglia by Strauss and Loewe and by Flexner and Amoss perivascular round-cell infiltrations and occasional hemorrhages.

It is not necessary to describe the details of cases such as have been mentioned, but instances of indubitable polyneuritis on an encephalitic basis are less common in the experience of the workers in Bellevue Hospital and the Neurological Institute than are the radicular types or those in which isolated nerve trunks such as the facial are alone involved.

J. D., a watchman, aged fifty-three years, formerly a coachman, a man who had never drunk more than an occasional glass of beer, in August, 1920, began to suffer from severe burning pains in the calf muscles, with tingling in the toes and progressive weakness in the legs. He became unable to walk and at the same time had severe headaches and felt very ill. He had a constant pyrexia of about  $2^{\circ}$  F. After two weeks the same symptoms as had been in the legs were felt in the arms, which gradually weakened. A month after these developments he began to see double, his pupils became unequal and sluggish to light, the left face became weakened, the facial expression grew masklike, he sweated excessively; the sleep mechanism was reversed—that is, he was drowsy by day and wide-awake by night—the pulse was persistently about 125 and the sugar content of the spinal fluid and its cell content were greatly increased. There was atrophy in the intrinsic muscles of both hands and fibrillary twitching in all four limbs. All deep reflexes were abolished. There was excruciating tenderness in the calf muscles and abolition of the sense of position in the feet and hands, with consequent sensory ataxia. There was no weakness in speech or swallowing. Micturition was slow and difficult, but there was no incontinence. This patient is making a slow recovery (December, 1920).

This case and two others in the neurological department at Bellevue Hospital remarkably resembled those reported before the American Neurological Association by myself under the caption "Acute Infective Neuritis." In them, however, it was unusual to have a cerebral symptom-complex, though autopsy examination revealed inflammatory lesions in the peripheral nerves, spinal ganglia and cord and cortex as well—lesions which for the most part, however, diminished as one ascended in one's examination.

These cases occurred as a minor epidemic among soldiers in the field; they had fever and other evidences of a general infection. In some few the posterior spinal roots were especially affected, so that root zones of grossly altered sensibility were easily demon-

strated. A constant feature of these soldiers was the peripheral paralysis of one or both sides of the face—a feature commonly but by no means constantly seen in the American cases of epidemic encephalitis.

In connection with these cases, however, we must consider those of acute polyneuritis occurring as a complication of malaria and of enteric fever and scurvy, and perhaps especially those recently described by Farnell in which a staphylococcal gastro-enteritis was promptly followed by acute polyneuritic symptoms with not infrequently fatal results. All these diseases differ from similar conditions found in the encephalitic epidemic in degree rather than in type, but make manifest that disease pictures are sketched and colored more by the varying natures of the structures attacked than by the specificity of the invading virus.

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### FURTHER OBSERVATIONS ON THE BLOOD-SUGAR TOLERANCE TEST AS AN AID IN THE DIAGNOSIS OF GASTRO-INTESTINAL CANCER.<sup>1</sup>

BY JULIUS FRIEDENWALD, M.D.,

AND

GEORGE H. GROVE, M.D.,

BALTIMORE, MD.

IN a study of the blood-sugar tolerance test as an aid in the diagnosis of gastro-intestinal cancer presented by us last year the following conclusions were noted.

1. There is present in carcinoma of the gastro-intestinal tract usually a rather characteristic curve of sugar tolerance which differs somewhat from that observed in carcinoma of other regions of the body. The curve of this affection usually presents a high sugar content even in the fasting state followed by an initial rise up to 0.23 per cent or higher within forty-five minutes after the ingestion of the dextrose remaining at this level for at least two hours, and rarely at any time during this period falling below 0.2 per cent.

2. The sugar-tolerance test is rather distinctive, so that it may render valuable assistance as a means of differential diagnosis between carcinoma and other diseases of the gastro-intestinal tract.

3. The opportunity has not been afforded to test a sufficient number of early cases of cancer of the stomach and intestines according to this method, so that as yet the value of this test as a means of early diagnosis has not been established; nevertheless, as

<sup>1</sup> Read at the Meeting of the Association of American Physicians, Atlantic City, May 11, 1921.



positive curves occur equally whether cachexia exists or not, or whether the extent of the involvement be slight or great, we are under the impression that the results may be quite definite even in the early cases of the disease. This question, however, requires further study.

4. While we fully realize that this test is not specific of carcinoma and cannot be relied upon alone without entering into the clinical aspects of the disease, and that there are cases of carcinoma in which negative findings occur or non-malignant conditions in which the results are positive, nevertheless we are of the opinion that when properly performed the blood-sugar tolerance test may be of considerable diagnostic help in obscure cases of carcinoma of the gastro-intestinal tract.

At that time our study included 32 cases of cancer of the gastro-intestinal tract, all of which presented the typical cancer curve. This curve was, however, not observed in any one of 55 other examinations, including 5 cases of carcinoma outside of this tract nor in 45 cases of benign affections of the gastro-intestinal tract, including peptic ulcer, syphilis of the stomach, diarrhea, dysentery, achylia gastrica, chronic gastritis, cholelithiasis, chronic appendicitis, enteroptosis, nervous dyspepsia and mucus colitis.

The typical cancer curve can easily be distinguished from that observed in other affections of the gastro-intestinal tract. It must be differentiated according to our observations from the normal curve, the atypical curve and the intermediate curve.

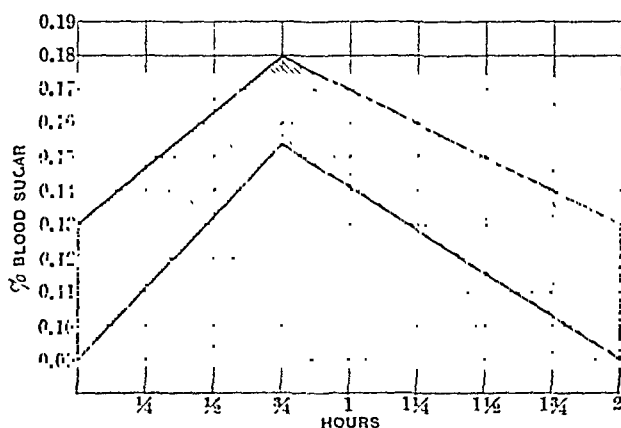


CHART I.—Maximum, minimum and average normal blood-sugar tolerance curve.

**The Normal Curve.** In normal individuals after the ingestion of 100 gm. of dextrose the blood-sugar content rises from 0.09 or even less to a height not usually above 0.165 per cent within forty-five minutes, falling usually more gradually within two hours to about the level as that observed in the fasting state. This character of

curve was observed not only in normal individuals but also in the non-cancerous digestive disturbances other than those which have been classified in the following groups.

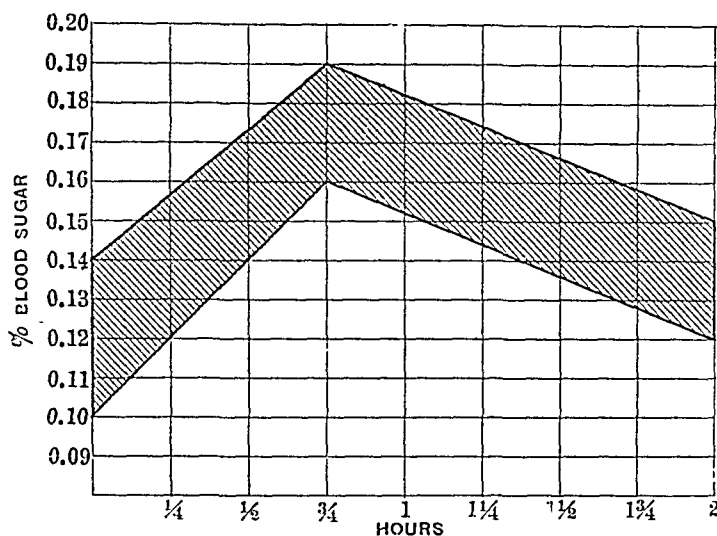


CHART II.—Maximum, minimum and average atypical normal curve.

**The Atypical Normal Curve.** In certain individuals, often those affected with an achylia gastrica, an atypical normal curve is observed in which the blood-sugar content presents practically normal values in the fasting state, ascending to a height of from 0.16 to 0.18 per cent within forty-five minutes after the ingestion of the dextrose, falling slowly within two hours to a level of from 0.13 to 0.15 per cent, but not any lower.

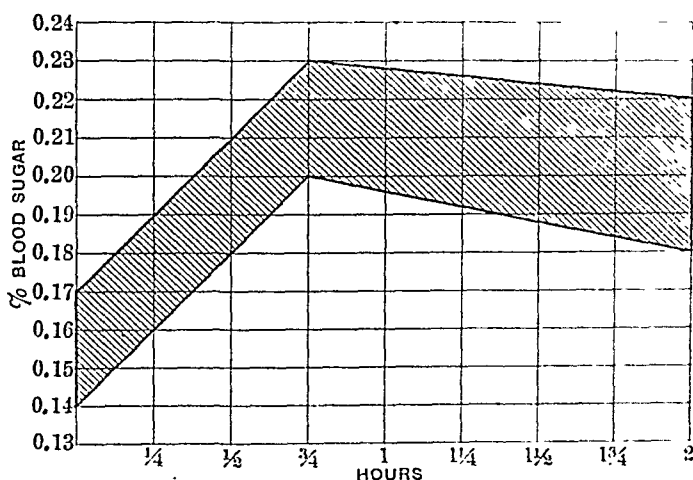


CHART III.—Maximum, minimum and average intermediate blood-sugar curve

**The Intermediate Curve.** The intermediate curve is usually observed in cases of carcinoma not associated with the gastro-

intestinal tract, in which the blood-sugar content presents comparatively high values even in the fasting state of 0.14 to 0.17 per cent,

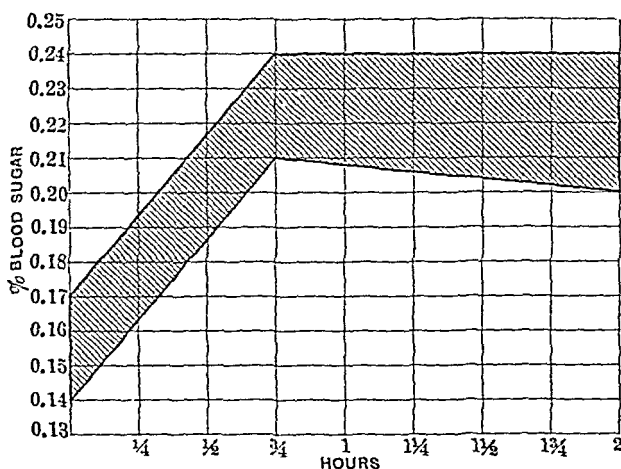


CHART IV.—Maximum, minimum and average blood-sugar tolerance curve in carcinoma of the gastro-intestinal tract.

and in which after the ingestion of 100 gm. of dextrose there is an initial rise to a height of from 0.2 to 0.23 per cent within forty-five

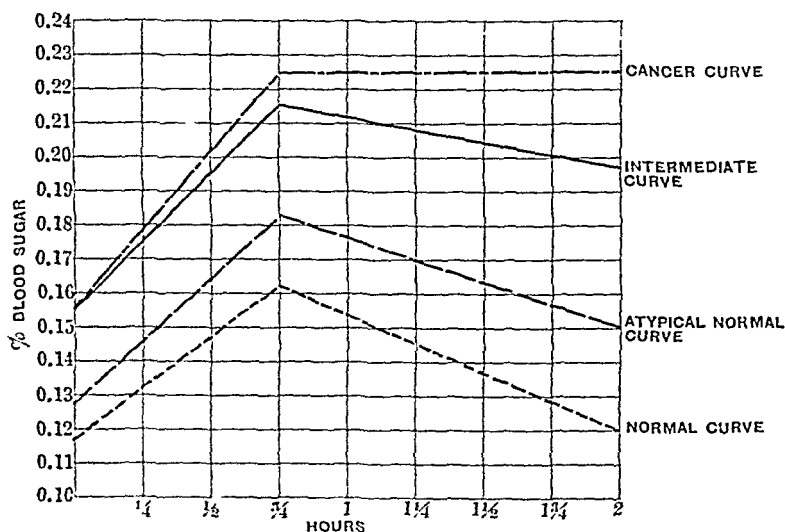


CHART V.

minutes, followed within two hours by a fall of from 0.18 to 0.21 per cent, never descending at this time to the level observed in the fasting state.

Since our former publication we have examined 43 additional cases of gastro-intestinal cancer, according to our method, totalling in all 75 cases. All were typical of the disease; of these 36 were operated on and the diagnosis was thus confirmed, and in the remaining cases there were definite palpable abdominal masses in addition to the usual physical signs present in this affection, and the examination of the gastric contents as well as the roentgen-ray findings and final outcome presented confirmatory evidence in every instance. Of these cases there were 47 of gastric carcinoma, of which there were 5 of cancer of the esophagus and cardia, 26 with obstructions at the pylorus, while 16 presented no obstruction. There were 5 cases of cancer of the colon, 2 of the pancreas, 8 of the liver, including 5 other abdominal organs; 3 of the rectum and 11 cases of carcinomatosis and 1 of the face and tongue.

In our examinations we followed the plan described in our former communication with the patient on a fasting stomach; blood was withdrawn for examination just before; in forty-five minutes; and two hours after the administration of 100 gm. of dextrose and the blood sugar determined by means of the Epstein method under the identical precautions described by us.

The character of curve present under these conditions in gastro-intestinal cancer is quite characteristic and can usually be distinguished from that observed in cancer of any other region of the body or from that in non-malignant diseases. It was noted in all of these cases of cancer of the gastro-intestinal tract but 3, of these 2 G. D. (No. 15) and M. P. M. (No. 50), were instances of general carcinomatosis and 1, C. I. (No. 33), a case of rectal carcinoma; in all the diagnosis was confirmed by operation and the curves presented were typically normal.

On the other hand there were 5 cases proved by operation to be non-malignant in which typical cancer curves were obtained; of these there was M. B. C., a case of tuberculous peritonitis; M. M. C., of gastric syphilis; B. H., of carcinomatosis; S. O., of cholelithiasis, and J. T. S., of gastric syphilis.

It is important to note that diabetes, nephritis, tuberculosis and disturbances of the thyroid should always be excluded before the tolerance test is undertaken, inasmuch as hyperglycemia is frequently present in these affections. However, as this test is to be utilized only as a means of differentiation between carcinoma and other diseases of the gastro-intestinal tract many conditions associated with hyperglycemia need not here be taken into consideration.

Inasmuch, therefore, as this test has proved positive in 72 of the 75 cases of cancer of the gastro-intestinal tract, there can be but little question of its value as a diagnostic measure even though it was found positive in 5 cases of non-malignant disease of these organs.

TABLE PRESENTING THE PERCENTAGES OF BLOOD-SUGAR OBTAINED  
IN SEVENTY-FIVE CASES OF CANCER OF THE GASTRO-  
INTESTINAL TRACT.

1.	A., F. C.	Cardia	.172	.260	.248
2.	B., C.	Pylorus	.164	.224	.230
3.	B., C.	Cardia	.192	.282	.250
4.	B., C.	Stomach	.141	.193	.172
5.	B., C.	Stomach	.140	.193	.172
6.	B., I.	Pylorus	.121	.197	.178
7.	B., B.	Pancreas	.159	.194	.198
8.	B., M. J.	Pylorus	.141	.250	.238
9.	B., G. F.	Liver	.120	.198	.192
10.	B., S. S.	Stomach	.163	.268	.278
11.	C., M. H.	Stomach	.196	.240	.243
12.	C., M.	Stomach and liver	.146	.230	.242
13.	C., T.	Stomach and liver	.147	.194	.191
14.	C., G.	Stomach	.162	.204	.201
15.	D., G.	Carcinomatosis	.142	.180	.150
16.	D., B.	Carcinomatosis	.156	.260	.268
17.	D., N.	Stomach	.170	.220	.224
18.	D., J. A.	Carcinomatosis	.161	.258	.255
19.	D., C. E.	Pylorus	.131	.187	.183
20.	D., D. E.	Stomach	.178	.364	.332
21.	F., S.	Rectum—before operation	.198	.198	.200
		after operation	.148	.188	.184
22.	F., M.	Liver	.120	.180	.200
23.	F., T. W.	Pylorus	.154	.226	.272
24.	G., M.	Carcinomatosis	.150	.186	.190
25.	G., E.	Intestines and uterus	.125	.187	.194
26.	G., D.	Carcinomatosis	.161	.250	.256
27.	G., H.	Liver	.163	.214	.208
28.	H., C.	Pylorus	.147	.192	.188
29.	H., I. L.	Liver	.154	.210	.206
30.	H., S.	Rectum and intestines	.172	.248	.280
31.	H., W.	Pylorus	.149	.198	.194
32.	I., C. S.	Cecum—before operation	.155	.226	.258
		after operation	.082	.170	.110
33.	I., C.	Rectum	.120	.167	.113
34.	J., P.	Pylorus	.142	.187	.179
35.	K., W. H.	Pylorus	.176	.282	.270
36.	K., B.	Pylorus	.132	.198	.214
37.	L., J.	Stomach	.148	.236	.232
38.	L., J. E.	Stomach	.198	.276	.264
39.	L., M. B.	Pylorus	.159	.191	.198
40.	L., F. C.	Stomach	.170	.268	.208
41.	L., F.	Rectum	.202	.300	.264
42.	L., J.	Pylorus	.176	.252	.266
43.	M., F.	Liver	.154	.200	.204
44.	M., R. E.	Stomach	.142	.194	.192
45.	M., P. J.	Pylorus	.116	.206	.192
46.	M., J.	Prostate and intestines	.157	.198	.172
47.	M., C. J.	Carcinomatosis	.158	.210	.210
48.	M., M.	Pylorus	.138	.204	.204
49.	M., H. T.	Pylorus	.136	.252	.280
50.	M., M. P.	Carcinomatosis	.120	.168	.127
51.	N., A.	Intestines	.154	.216	.220
52.	P., G. C.	Stomach	.164	.242	.238
53.	P., L.	Cardia	.168	.204	.192
54.	P., M. G.	Stomach	.152	.198	.200
55.	P., T.	Carcinomatosis	.171	.234	.242
56.	P., H. G.	Stomach	.142	.262	.247

57.	R., E.	Pylorus	.141	.192	.174
58.	S., E. P.	Bladder and liver	.160	.245	.238
59.	S., F. L.	Tongue	.384	.497	.497
60.	S., C.	Carcinomatosis and liver	.162	.198	.200
61.	S., I. P.	Carcinomatosis	.121	.162	.153
62.	S., M.	Cardia	.131	.180	.224
63.	S., C.	Stomach	.206	.266	.256
64.	S., L.	Cardia	.178	.234	.228
65.	T., J. T.	Pylorus	.171	.239	.240
66.	T., M.	Carcinomatosis	.171	.214	.204
67.	V., S.	Stomach	.138	.214	.206
68.	W., C.	Pancreas	.160	.224	.198
69.	W., C. C.	Pylorus	.156	.230	.218
70.	W., L. H.	Stomach	.168	.290	.270
71.	W., S.	Pylorus	.162	.198	.194
72.	W., E.	Stomach	.154	.192	.178
73.	W., V.	Pylorus	.164	.198	.224
74.	Z., V.	Pylorus	.152	.236	.240
75.	Z., W. A.	Pylorus	.161	.220	.218

The value of this test is well illustrated in 3 cases of this series. We append a brief abstract of the histories of these cases.

CASE I.—S. B. (No. 2112), female, aged sixty-seven years, had been complaining of digestive disturbances for many years. Her appendix had been removed in 1908 with marked relief, but during the following year symptoms were again noted in the form of acute attacks of pain in the upper right quadrant, which were severe at times and were accompanied by nausea, vomiting, chills and fever, but without jaundice. Recently the attacks had become more frequent, but not quite so severe as formerly, though during the past two weeks there was continuous distress in the abdomen accompanied with nausea and vomiting. Loss of flesh and great prostration were also noted. At this time the liver had become markedly enlarged and quite tender on pressure. The diagnosis of cholecystitis was made even though the blood-sugar tolerance test revealed a typical cancer curve. At operation numerous adhesions were detected in the upper right quadrant region and the gall-bladder was found to contain a thickened, ropy, infected bile, and cholecystectomy was performed. The patient recovered from the effects of the operation, but after several weeks nausea, vomiting and abdominal discomfort manifested themselves. Symptoms of pyloric obstruction were now noted with vomiting of the retention type. A month following the first operation a second was performed for the relief of the pyloric obstruction, when a large carcinoma was observed involving the pylorus and liver.

CASE II.—C. S. I. (No. 5091), male, aged fifty-four years, had been affected with indigestion for four months. At the onset he was taken with an acute attack of pain in the lower right quadrant of the abdomen and a diagnosis of acute appendicitis was made; since then there had been constant indigestion, with general discomfort in the abdomen, pressure, distention, loss of appetite,

In the duodenal contents pancreatic ferments were very deficient. There was feeble amyolytic enzyme, still feebler proteolytic enzyme and usually absence of lipase action. Always there was mucus in excess, occurring often in shreds, containing numerous pus cells, at times many degenerated red blood cells.

It was evident that there was an open passage through the bile ducts, but nevertheless infection coming through the biliary channels. This was proved by the use of the duodenal tube after irrigation of the stomach and duodenum. It was also evident that there was a very defective digestive power in the duodenum as result of the disordered pancreas and the duodenitis. At this time the suggestion was made by Dr. Rose Donk, who was assisting on the case, that the transfusion of normal duodenal contents from a healthy donor might provide the patient with needed digestive ferments and help her to gain in nutrition. This treatment was carried out by Dr. Donk under my observation during a period of two weeks. The healthy donor while fasting, having had passed the duodenal tube and having had the secretions stimulated by small quantities of hot water, gave out from 60 to 200 cc of duodenal contents, which were immediately introduced through a tube into the duodenum of the patient. The result of this treatment was published by Dr. Donk,<sup>2</sup> under the title "Transfusion of Duodenal Contents." The work was interesting, and unquestionably the patient received temporary benefit from the measure. I am convinced that this suggestion made by Dr. Donk will prove to be of some practical importance in selected cases.

Intestinal perfusion was also practised at other times, with apparent benefit. A freer flow of bile was promoted by irrigation with magnesium sulphate solution as suggested by Meltzer. The diarrhea never recurred with its former intensity, yet there was a continued predisposition to looseness requiring attention and at times special medication. The sigmoidoscope revealed a catarrhal colitis but no bleeding-points. The patient in February had a definite intestinal hemorrhage unexplained in origin.

Medical and surgical consultants leaned to the opinion that there was more trouble in the gall-bladder than had been hitherto believed. It was suggested that we were dealing with a chronic cholecystitis with calculi. There was no evidence of this, however, in the radiograms which were shown and discussed at our last meeting. To my mind it seemed clear that the trouble was not from the gall-bladder, but that we had, following the blocking at the papilla in the beginning of the jaundice, an ascending infection which reached the liver and probably the pancreas.

During May the case was at a standstill, with an occasional discouraging relapse; that is, chills, fever and leukocytosis, the

<sup>2</sup> Jour. Am. Med. Assn., November 13, 1920.

attack lasting two or three days; then the jaundice would fade, but it never disappeared. It was decided, finally, that there should be made a cholecystostomy, with the hope that by removing a cholecystitis the infection passing into the intestine would be eliminated and that the patient might be benefited. Also, it would settle the question as to calculi.

The operation was made under gas and ether anesthesia, which was preceded by a transfusion of 750 cc of blood from a well-typed donor. The transfusion was intended not only to strengthen the patient but to increase the coagulability of the blood, which had been found to be fourteen minutes plus. Following the transfusion, Dr. James A. MacLeod operated upon the patient, removing the appendix, which showed chronic inflammation, and performing cholecystostomy. It was decided to do little exploring, so that the shock might be at the minimum. However, it was found that there was no evidence of tumor about the stomach or duodenum; the pancreas was unusually firm on palpation; the gall-bladder was not distended but was rather pale, and contained no calculi, but a small amount of rather dark bile of increased consistency. The liver was apparently moderately enlarged, pale yellow in color, rather firm upon palpation, with the surface irregular as seen in cirrhosis. The common duct was not explored.

The patient endured the operation remarkably well and seemed to be in better condition after it than before, doubtless from the transfusion. The amount of bile drainage was small and we felt that little was directly gained by the operation. For some days, however, the patient did well, when there ensued another, and this time severe, intestinal hemorrhage, and transfusion seemed necessary to save life; 500 cc of blood were therefore introduced into a vein. The blood was taken from a new donor. There was no agglutination shown on typing, but subsequently it was found that the patient's serum hemolyzed the donor's corpuscles. There followed great prostration, with unconsciousness. In the state of depression, amounting almost to shock, which followed the second transfusion with blood, there appeared in the urine a large amount of urobilin. Previously it never had appeared in the urine, and after that event it never disappeared. It is an interesting question as to what effect this transfusion may have had upon the liver to hasten its degeneration in its already crippled and infected state. There is, of course, the possibility of coincidence, but the clinical fact remains striking. For a few days it looked as though the patient would succumb from hemolysis and protein-poisoning. However, she rallied and matters progressed favorably for a few days, although there continued to be marked urobilinuria. At this time drainage of bile was insignificant, and it occurred to me that benefit might follow irrigation of the gall-bladder through the drainage tube, with a magnesium sulphate solution of 25 per



and one was stillborn. Four died of gastroenteritis. No other boys are living. One sister living, none dead. The patient was admitted to the children's ward of the Protestant Episcopal Hospital November 7, 1920.

*Personal History.* Had measles and whooping-cough five years ago. Two months ago had an attack of acute rheumatism and one month later had tonsillitis. No other illnesses. No operation or injuries.

*Present Illness.* The chief complaint was pain in the abdomen. Began about three days ago with fever and vomiting, but when it began there was no pain in the abdomen. On the second day his condition continued the same; the child was more feverish and complained somewhat of shortness of breath. On the third night he began to complain of pain in the abdomen. The mother does not know whether pain was localized or diffuse. Vomiting continued. The mother stated that the child had vomited twenty times during the day. The bowels moved four times during the fourth day.

*Examination.* The patient was a well-developed young child. Had rapid breathing, with the face slightly flushed, and a short cough. Head negative, face congested and teeth in fair condition. Breath sounds are lessened over the left lower lobe laterally. Heart shows a very loud mitral murmur. The abdomen seems tender on both sides. No rigidity.

The pulse is rapid; the precordia is bulging. The abdomen is normal in shape. The cardiac impulse is diffuse over the precordia; the apex-beat is at the upper line of the fifth interspace. Heart dulness extends to the midline of the sternum, to the anterior axillary line and apparently runs up to both clavicles. Higher pitched note over the left clavicle than over the right. Typical pericardial friction is heard. A systolic murmur also is heard in the mitral area. Breath sounds are much louder in the left axilla than in the right, in addition to what appears to be a pericardial friction rub and a pleuropericardial murmur heard at the angle of the left scapula. The lungs are apparently normal. No tubular breathing and no bronchophony. The abdomen is resistant, distended and tender. There is most marked tenderness and resistance in the region of the appendix. So great and prominent are the appendicular signs that the surgeon in consultation made a diagnosis of appendicitis. Peristalsis is present.

February 4, 1920. Friction is evident and superficial. Tubular breathing posteriorly over the left chest at the angle of the scapula. Vocal fremitus is increased.

February 5. The abdomen is soft; no pain. All the abdominal symptoms have disappeared.

February 8. Blowing breathing at the angle of the left scapula still continues. There are no signs of abdominal distention today. Pericardial friction is still evident.

February 9. Dulness over the right edge of the sternum at the

upper border of the second rib, just outside of the nipple line. Still area of dulness at the angle of the scapula. Still blowing breathing and bronchophony.

February 11. Pulse is rapid and feeble. Friction sound is evident in front. Dulness in the right axilla. Blowing over practically the whole base posteriorly.

February 13. Tap of the pericardium in Rotch's notch positive today and 35 cc of fluid were removed. Heart dulness is to the right of the sternum in the axillary line. Heart action still rapid. Friction still present; not as much blowing as yesterday. Still marked blowing at the angle of the scapula.

February 14. Patient's condition is much worse. Breathing is more labored; pulse is imperceptible; face is pale. Cyanosis around the lips. Rales in the chest. Heart sounds indistinct.

At 3.30 P.M. the patient's condition is unimproved. Died at 5.20 P.M.

*Autopsy.* The heart was found to be enlarged. There was no fluid in the pericardium; there was a typical "butter-fat" appearance of the exudate in the pericardium. The pericardium was adherent to the lung posteriorly. The appendix was normal and there was no evidence of past or present inflammatory condition.

Recently the senior author saw a case with typical symptoms and physical signs of a large pericardial effusion.

Two weeks previously the patient had been seized with abdominal symptoms significant of appendicitis. An operation was performed. According to the operator the appendix was mildly inflamed, with some lymph on its exterior surface. Immediately after the operation the child developed a well-marked pericarditis. Here, then, is a case in which a pericarditis was coexistent with appendicitis, showing that care must be exercised in differentiation, bearing in mind that an appendicitis and pericarditis can coexist. The question of operation or no operation will then have to be decided upon the merits of the individual case.

So far as our knowledge goes, writers generally speak of pain as one of the symptoms of pericarditis. This pain may be conducted to the epigastrium. McFederan<sup>1</sup> speaks of severe epigastric pain with immobility of the diaphragm and nausea and vomiting.

Fussell<sup>2</sup> speaks of the pain present in pericarditis being sometimes referred to the appendicular region and also calls attention to the occasional difficulty of differentiating appendicitis and pericarditis. He<sup>3</sup> calls attention to the necessity of differentiating appendicitis from pericarditis.

Wynter<sup>4</sup> says that in a majority of the cases affecting the lung

<sup>1</sup> Osler and McCrae: *Modern Medicine*.

<sup>2</sup> Pericarditis, Tyson's *Practice of Medicine*.

<sup>3</sup> *Monographic Medicine*, 5.

<sup>4</sup> Absence of Abdominal Respiratory Movements as an Indication of Pericarditis, *Clinical Journal of London*, 1913.

and the pleura the abdominal breathing is one-sided, whereas the influence on abdominal movement in pericarditis is bilateral, and hence absence of abdominal movement in pericarditis is as obvious as in abdominal conditions, though rigidity and tenderness are for the most part lacking in pericarditis.

He reports two cases in which remarkable stillness of the abdomen led to the diagnosis of perforated gastric ulcer in one case and of appendicitis in the other. The case of supposed appendicitis was operated upon and a normal appendix was removed without adhesions.

He concludes that in a case in which the loss of abdominal movement is marked in the absence of an obvious lung or abdominal lesion, pericarditis should be considered.

The explanation given by Mackenzie<sup>5</sup> for the transference of pain in visceral diseases is as follows:

1. Stimuli which produce pain in the external body wall are not adequate to produce this sensation when applied to the viscera

2. Violent contraction of a non-striped muscle fiber produces pain, but that the region in which the pain is felt is different from that in which the contracting muscle lies, and that when a sensory muscle is stimulated in any part of its course in the brain, the cord, or the trunk of the nerve the pain is distributed to the peripheral distribution of the nerve in the external body wall. This is his so-called viscerosensory reflex.

He further considers that in order to call into effect this viscerosensory reflex there must be an adequate stimulus, and one may consider that because the stimulus is rarely adequate in pericarditis, pain in this condition is not always transferred either to the arm, the epigastrium (which is the most common seat of referred pain) or to the lower abdominal wall, which is the rarest seat of localization of the pain.

His visceromotor reflex may explain the rigidity of the abdominal wall in these cases.

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## PERICARDITIS IN CHRONIC NEPHRITIS.\*

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ALTHOUGH the occurrence of acute pericarditis in advanced renal disease has long been known the mechanism of its origin is still obscure. Interest in the subject was aroused by a recent case. The patient was a girl, aged nineteen years, suffering from an end-stage chronic nephritis. After the development of a severe acidosis

<sup>5</sup> Diseases of the Heart.

\* From the Medical Clinic of the Presbyterian Hospital, New York.

and a fibrinous pericarditis she finally succumbed. When at the suggestion of Dr. Longcope other cases of acute pericarditis in nephritis were reviewed it was found they fell into a recognizable group having fairly well-defined clinical and laboratory characteristics. The pathogenesis of the pericarditis was further studied by correlating the bacteriological with the pathological findings. The facts brought out were thought to throw an additional light upon the etiology of the complication.

In the cases of renal disease originally described by Bright<sup>1</sup> (1836) acute pericarditis is listed in 8 out of 100 autopsies. He regarded it as part of a general tendency toward involvement of the serous membranes. In the same series the pleura was acutely involved in 16 cases and the peritoneum in 12. Special emphasis upon the frequency of pericarditis in chronic nephritis was given by Taylor<sup>2</sup> (1845), who described it in 5 out of 51 cases that he examined post mortem. It is interesting to note in passing that five years later Taylor concluded that whereas practically all the cases of rheumatic pericarditis got well those following renal disease were uniformly fatal. Von Bamberger<sup>3</sup> states, according to his own observations, that 14 per cent of cases of Bright's disease develop pericarditis. The incidence given by other writers varies. Rosenstein<sup>4</sup> 7 per cent, Frerich<sup>5</sup> 4.5 per cent, M. Rayer<sup>6</sup> 5.4 per cent. Sibson<sup>7</sup> made an exhaustive study of the subject and in 1691 collected cases of nephritis found the incidence 8.1 per cent. In his personal series of 285 cases there were 25 cases of acute pericarditis, or 8.8 per cent. Sibson mentions 2 cases of this latter group occurring in acute nephritis and the remainder in chronic nephritis.

In the autopsy group here presented of 162 cases of nephritis 18 had acute pericarditis, or 11.1 per cent. In a clinical group represented by cases of nephritis admitted to the hospital during the corresponding period, out of 929 cases there were 30 who developed pericarditis, or 3.2 per cent. The latter figure may be said to express the incidence of the complication in non-fatal and fatal nephritis, the autopsy statistics naturally representing the incidence in fatal cases alone. Approached from the viewpoint of the causes of pericarditis in general, Sears<sup>8</sup> found chronic nephritis operating as a factor in 7 out of 100 cases, or 7 per cent; Preble,<sup>9</sup> analyzing 300 cases in 11.2 per cent. Locke<sup>10</sup> studied pericarditis as it occurred in 3683 routine autopsies; 4 per cent of all autopsies showed an acute pericarditis. Evidence of this complication in the clinical notes was present in 17 per cent. In 150 autopsies of acute pericarditis 16 were associated with nephritis, or 11 per cent. Of these 8 were grouped as fibrinous pericarditis, 6 adhesive (total or partial) and 2 purulent. Hirschfelder<sup>11</sup> states that pericarditis occurred in 230 (1 per cent) of the cases admitted to the medical service of the Johns Hopkins Hospital. Of these 33 were associated with nephritis, or 14.3 per cent. According to the statistics of these authors,

nephritis comes third as a cause of pericarditis, pneumonia and rheumatism only being more frequent. Sinnhuber<sup>12</sup> places rheumatism first, nephritis second, and the pyogenic infections afterward.

Concerning the pathogenesis of this complication in nephritis standard text-books are either non-committal or at variance with each other. Whether the cause lies in chemical irritation or secondary infection remains undetermined, as expressed by Gibson.<sup>13</sup> Aschoff<sup>14</sup> makes a similar statement. MacCallum,<sup>15</sup> speaking of the frequent occurrence of pericarditis in nephritis, says, "In these cases it is generally difficult to find any bacteria." Hirschfelder<sup>16</sup> states that "it is usually due to an intercurrent infection, and the pyogenic cocci can often be cultivated from the exudate." According to Wells<sup>17</sup> "the uremic pericarditis and endocarditis, which have often failed by ordinary methods to yield any bacteria, are apparently toxic processes." Sinnhuber<sup>12</sup> (1911) says that since neither cultures nor microscopic researches have shown bacteria it is apparently a toxic inflammation.

The clinical group comprises 30 cases. As all the factors studied were not present in every case the proportion of each will be mentioned. The laboratory data collected were selected at or near the onset of the pericarditis in order that they should represent factors which perhaps predisposed toward the complication. They are not then the most extreme findings, and are not at all in most instances antemortem statistics. This will be seen more clearly when the duration of life, after development of the pericarditis, is discussed.

The patients were mostly just below middle age, the average age being thirty-seven years, the extremes fifteen years and fifty-seven years. There were an equal number of males and females. All were diagnosed chronic nephritis. No case of acute nephritis developed the complication, nor was there a case of pure salt-and-water retention nephritis (nephrosis). The cardinal features included a uniformly marked elevation in blood-pressure; a severe secondary anemia; moderate leukocytosis and polynucleosis; a distinct hemorrhagic tendency; a greatly increased blood-urea nitrogen; minimal phenolsulphonephthalein excretion and a conspicuous acidosis.\*

\* Acidosis is used her to mean a lowering of the bicarbonate reserve of the blood and does not necessarily indicate any change in the H-ion concentration. In these cases the diminution in available alkali no doubt arose through an increase in non-volatile acid. It is, of course, impossible to say by a determination of the plasma CO<sub>2</sub> whether the H-ion concentration of the blood persisted normal or underwent an actual shift in the acid direction, *i. e.*, whether the acidosis was compensated or uncompensated. (Terms originally used by Hasselbach, K.A., and Gammeltoft, S.A., *Biochem. z.* 1915, 68, 205, and adopted by Van Slyke, Donald D., and Cullen, Glenn E., *Jour. Biol. Chem.*, 1917, 21, 293). This important point can in the future be satisfactorily determined by constructing the so-called carbon dioxide diagram of the blood. (Haggard and Y. Henderson (*Jour. Biol. Chem.*, 1919, 39, 163). It has recently been applied to a series of hospital patients by Means, Bock and Woodwell (*Jour. Exp. Med.*, 1921, 32, 201), and its value in determining actual changes in blood reaction has been demonstrated.

The average blood-pressure of the 30 cases was 214/136, the lowest 170/110. The average red blood cell count of 22 tested cases was 2,738,000, the hemoglobin 48 per cent. In no case was there absence of anemia. The majority of the cases showed a moderate leukocytosis, with polynuclear predominance at the time of development of the pericarditis. The average of 29 cases was 15,900 for the white count, polynuclears 87 per cent; 2 cases only showed a white blood count under 10,000. The temperature was variable, often showing a slight elevation, rarely more than 1° or 2°. A distinct tendency to hemorrhage was noted in 21 of the 30 cases, or 70 per cent. This varied in degree and was manifested in various ways, commonly as petechiæ, purpura of the skin or mucous membrane, epistaxis, hematemesis and rectal hemorrhages.

The average blood urea of 28 cases was 2.69 gm. per L. All were considerably elevated except one case, (No. 29), which had 0.45gm per L. This patient had general arteriosclerosis with a blood-pressure of 300/200, albumin and casts in the urine without fixation of the specific gravity, and, in addition, aortic valvular heart disease. The pericardial friction lasted four days and the patient improved and left the hospital. He died one and a half months later at home. The nephropathy here would perhaps be grouped as an arteriosclerotic kidney. Elevation of the blood urea in cases of nephritis with acute pericarditis has been commented upon by French authors (in the French, "pericardite brightique"). In a series of 11 cases of Vidal and Weil<sup>18</sup> the average was 2.71 gm. per L. Chalièr and Novi-Jusserand<sup>19</sup> report 1 case in full in which the blood urea was 2.10 gm. per L. Other individual cases are mentioned by d'Ulrici,<sup>20</sup> 4.85 gm. per L., Froment and Rochaix,<sup>21</sup> 3.57 gm. per L., and Foy<sup>22</sup> 2.54 gm. per L. In comparing the average of this series, 2.69 gm. per L., it must be remembered that this value does not represent the maximal values of the cases, but the finding on or near the day when the pericardial rub first became evident. As will be emphasized later the blood urea progressively mounted. (See Table I for clinical data.)

In all of the 16 cases in which observations were made an acidosis, as evinced by a lowering of the plasma bicarbonate, was present. In 9 cases the figures were obtained by the carbon dioxide combining power of the plasma by the method of Van Slyke,<sup>23</sup> and averaged 28.7 vol. per cent. In 7 earlier cases the results are recorded by the carbon-dioxide tension of the alveolar air (Fridericia method), and averaged 24.59 mm. Hg. The lowest observation was 11.8 vol. per cent, plasma CO<sub>2</sub>. (Some of the cases at times showed lower figures than are listed in the table, but here too those were selected which had the nearest time relationship to the onset of the pericardial friction.) A conspicuous diminution of the available blood alkali is thus evident from both methods. That most patients with advanced nephritis, especially in the last stages of

TABLE I.—CLINICAL DATA.

Case.	Age.	Sex.	B. P.	W. B. C.	Diff. polys., per cent.	R B. C.	Hrb., per cent.	'Bl. urea, gms per L.	Bl. CO <sub>2</sub>	Phthalein, per cent.
1 E. P.	48	F	214/105	19,000	88	2,200,000	60	3.92	31.2 vol. per cent	8.0
2 W. D.	50	M	210/150	13,000	88	1,000,000	15	2.50	26.6 mm. Hg.	0
3 J. G.	36	M	224/130	24,000	92	3,000,000	47	2.50	19.7 "	0
4 C. L.	49	F	200/140	18,200	92	3,200,000	64	3.73	"	0
5 D. V.	44	M	208/126	16,000	86	3,000,000	50	2.70	19.2 "	0
6 W. F.	26	M	226/140	19,000	86	2,620,000	52	2.91	"	0
7 C. A.	29	F	215/145	29,000	89	3,350,000	50	3.07	"	0
8 M. E.	40	F	214/136	.....	..	.....	..	1.50	"	0
9 T. L.	44	M	222/150	15,200	88	3,736,000	70	3.87	38.5 vol.	0
10 C. K.	15	M	200/130	23,700	80	2,912,000	40	4.45	22.1 "	0
11 A. K.	40	F	205/130	6,000	75	3,480,000	70	3.11	24.0 "	0
12 W. S.	37	M	170/135	14,000	80	4,000,000	55	1.58	47.0 "	15
13 E. S.	21	F	170/110	11,200	89	1,700,000	20	4.98	32.8 "	1
14 T. S.	50	M	220/122	13,000	80	3,500,000	50	4.12	21.4 "	1
15 L. M.	19	F	180/110	10,200	68	1,300,000	30	2.95	11.8 "	7
16 T. S.	48	M	218/110	23,800	91	3,400,000	55	1.85	25.2 mm. Hg.	7
17 H. W.	19	F	178/110	11,500	88	1,475,000	32	2.50	22.75 "	34
18 A. W.	40	F	244/152	13,800	84	.....	..	2.61	"	0
19 R. A.	48	M	210/148	12,000	67	.....	..	1.77	"	10
20 M. G.	36	F	220/180	9,400	82	.....	50	3.72	"	3
21 L. L.	38	M	210/138	14,100	72	.....	70	2.20	"	10
22 H. P.	41	M	210/140	20,000	83	.....	..	.....	"	10
23 L. J.	36	F	176/90	8,460	74	1,480,000	30	.....	"	3
24 R. T.	35	F	195/100	17,000	90	1,828,000	38	2.44	30.5 vol. per cent	0
25 E. S.	32	F	255/175	19,800	92	2,380,000	45	3.14	"	6
26 B. G.	37	M	230/150	15,150	89	4,000,000	69	1.60	"	9
27 E. H.	46	F	250/140	14,500	74	3,500,000	46	1.75	"	15
28 J. E.	57	M	212/140	17,200	90	.....	..	1.14	29.45 mm. Hg.	15
29 L. H.	42	F	300/200	15,000	76	.....	..	0.45	"	5.9
30 Y. F.	29	M	228/162	19,000	95	2,584,000	42	2.27	29.25 "	5.9
Average	37.8	M50%	214/136	15,936	87	2,738,409	48	2.69	28.7 vol per cent 24.59 mm. Hg.	

the disease, have a demonstrable acidosis has been shown by Henderson and Palmer,<sup>24</sup> Peabody,<sup>25</sup> Chace and Myers<sup>26</sup> and others. According to the figures of this series 100 per cent of the tested cases had an acidosis at the time of onset of the pericarditis, in most instances of severe grade, represented as it was by an average plasma  $\text{CO}_2$  of 28.7 vol. per cent.

The average phenolsulphonephthalein excretion in 20 cases was 5.9 per cent; in one-half of these it was zero. No proportional relationship could be established between the degree of acidosis, the elevation in blood urea or the excretion of phthalein. This is in accordance with the similar earlier observation of Peabody.<sup>25</sup>

In 26 of the 30 cases a pericardial friction-rub was described in the clinical notes. In 1 additional case the diagnosis was made by signs of effusion. The diagnosis was thus made clinically in 90 per cent of the cases. The frequency with which the diagnosis was made by a friction-rub may perhaps be accounted for by the small amount of pericardial fluid that is present in this type of pericarditis (as will be seen later). The average duration of the rub was eight days;\* in one case it could be heard for two and a half months. The average length of life after the appearance of the rub was twenty-nine days. One patient, in whom the pericardial friction lasted nine days, lived for one year thereafter. If this case were not included the average length of life after the rub became evident would be sixteen days. Another patient lived two months after the onset of the pericarditis; a third two and a half months, and a fourth four months. This is mentioned to emphasize that the pericarditis is not always a terminal complication. It may subside and the patient undergo a remission of symptoms, leave the hospital and perhaps live comfortably for several months. The case mentioned above that lived for one year showed at autopsy an adherent pericardium.

The pericarditis does not seem to be the direct cause of death in many of these cases. In some of them it seems related rather to the increasing retention of nitrogen in the blood. The acidosis too does not appear responsible for the final succumbing of the patient. In these cases it was generally combated with sodium bicarbonate whenever it became dangerously low. The case of L.M. may be taken as an example: At the time of her admission to the hospital, when the pericarditis was first noted, the blood urea was 2.95 gm. per L. and the plasma  $\text{CO}_2$  11.8 vol. per cent. The friction-rub persisted until death, sixteen days later. Bicarbonate was persistently administered, aiming to keep the blood  $\text{CO}_2$  at least above

\* It must be remembered that the duration of the rub applies to hospital residence. In some cases the rub was present on admission and an accurate estimation of its actual duration is thus not possible.



40 vol. per cent. The determinations ran as follows: 11.8 vol. per cent, 10.9 vol. per cent, 27.1 vol. per cent, 48.1 vol. per cent, 40.4 vol. per cent, 46 vol. per cent. At the same time the blood urea mounted 2.95 gm. per L., 3.17 gm. per L., 3.55 gm. per L., 4.75 gm. per L. The cause of death did not seem linked with progressive heart failure nor obviously with the acidosis, but rather with the progressive retention of nitrogen in the blood.

Of the 30 cases 18 came to autopsy. The kidney lesion was predominantly the contracted granular kidney, more commonly the glomerular than the arteriosclerotic contracted kidney. Sibson's<sup>7</sup> cases occurred very largely in the small granular kidney. Lecorche and Talamon<sup>27</sup> also believed pericarditis to be more frequent in this interstitial form of the disease. According to Grainger Stewart<sup>28</sup> however, it was equally common in the parenchymatous and renal cirrhosis. No attempt has been made in this series to correlate the anatomical lesions with the clinical grouping of the nephritis.

The pathology of the pericarditis possesses special interest because of its relation to some of the bacteriological findings. The pericardial cavity contained in most instances a little increase in fluid, 12 of the 18 cases having between 50 and 200 cc; 2 showed no fluid; 1 had an adherent pericardium; 3 had a large excess of fluid; in 1, 700 cc of bloody fluid; another that had been tapped during life contained 2000 cc of dark red fluid in the pericardial cavity. Chalié and Novi-Jusserand's<sup>29</sup> case had 250 gm. and Widal and Weil's<sup>30</sup> cases between 50 and 250 gm. of pericardial fluid. The fluid was usually of a light or dark amber color, clear or only slightly turbid. Fibrinous adhesions were almost always present, appearing either as thin delicate bands or as a fine fibrinous deposit. Microscopically the fibrin network was free from cells beyond occasional scattered round cells. The epicardium, as a rule, was a little thickened and in the majority of cases contained a slight to a moderate infiltration of small mononuclear cells—in a few instances no infiltration at all. In 2 cases the mononuclear infiltration extended into the muscle substance. In 5 cases, however, a polynuclear infiltration was present, with smaller numbers of mononuclear cells as well. In 4 of these the polynuclear infiltration was present in the pericardium. In 1 case the pericardium was infiltrated moderately with mononuclear cells, but the smear of the pericardial exudate showed pus, blood cells and bacteria. Of the 5 cases showing polynuclear infiltration 4 were cultured, and all of these showed the presence of pyogenic organisms. The fifth had a sterile blood culture, but no culture had been made from the pericardium. In 2 of the cases the organisms were recovered in pure culture, one a hemolytic *Staphylococcus aureus* and the other a short-chain streptococcus. The third showed *Staphylococcus albus* and *B. coli communis*; the fourth, a non-hemolytic streptococcus, a bacillus belonging to the

Friedländer group and a Gram-negative bacillus which did not form gas with dextrose. In 2 of the cases in which a blood culture was done at the same time the same organisms were recovered, indicating there was a terminal septicemia, the pericardium constituting a localization of the infectious process. In the remaining 12 cases in which polynuclear infiltration was not demonstrated there were 4 cases that were tested bacteriologically and the pericardium found free from infection in all. There was 1 of these cases that had a terminal bronchopneumonia in which the lung culture at autopsy yielded a pneumococcus IV, but in which the pericardium was sterile both in aerobic and anaerobic culture. (See Table II for bacteriological and pathological data.)

It is interesting even in this small group that the 4 cases with frank infection showed a polynuclear response in the epicardium or in the pericardial exudate, whereas the 4 cases in which no infection of the pericardium was present showed an absence of polynuclear leukocytes, and, instead, mononuclear infiltration or no cellular infiltration whatsoever. Of the 4 sterile cases, in 3 the cellular response in the pericardium varied from just a few scattered mononuclear cells to a moderate infiltration. In the fourth only the pericardial fluid and fibrin tags were available, and these showed no cells at all. This division of cases brings forth the obvious suggestion that there may actually be two distinct etiologies for the complication, an infectious and a non-infectious. Before this is further discussed the bacteriological findings in the literature as well as the experimental evidence will be reviewed. This has been delayed up to this point in order that the histology of the pericarditis might be compared with the bacteriological findings on the basis of the above results. No purposeful comparison has previously been made, nor do many of the reports contain the material for doing so.

The review of all authentic reports concerning the bacteriology of pericarditis in nephritis shows 33 in which the bacteriology of the pericardium was investigated (31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42). Except for the more recent article by Widal and Weil most of the studies were made before many of the more recent methods of bacteriological research were instituted, and therefore have only a limited value. Of these cases, however, 18 were sterile and 15 showed bacteria, usually of the pyogenic variety. The most frequent invader was the pneumococcus and the next frequently found was the *Bacillus coli* and the streptococcus. The attempt to link up the histology of the pericardium with the bacteriological findings in the cases previously reported yields a partial confirmation of the results in our series. When infection was present polynuclear leukocytes were described in the pericardium or pericardial exudate in each instance in which individual case reports were given.

TABLE II.—PATHOLOGICAL AND BACTERIOLOGICAL DATA.

Cave.	Duration of rub, days.	Length of life after onset of pericarditis, days	Chest involvement.	Tendency to hemorrhage.	Pathology of pericardium.	Bacteriology.
1 E. P.	1	3	None	Moderate hematome- sis blood in stool.	Autopsy by Dr. Lamb, 100 cc pericardial fluid, amber, and slightly turbid. Strands of fibrin cover pericardial sur- faces. Petechial hemorrhages on visceral pericardium. Mi- croscopical lymphocytes, poly infiltration and edema.	Smears from pericardial fluid at autopsy showed a non-hymo- lytic streptococcus, a bacillus belonging to the Friedländer group, and a gram negative bacillus which does not form gas with dextrose. (Air was found in blood vessels in this case.) No cultures of pericardium.
2 W. D.	3	3	Pleurisy	Marked; rectal hem- orrhage; brain hem- orrhage; skin pete- chia.	Autopsy by Dr. Evans. Large excess of cloudy yellow fluid. Fine diffuse fibrinous deposit. Microscopical fibrin is scanty and contains a few round cells. No autopsy.	No cultures of pericardium.  Two blood cultures during life sterile. No cultures of peri- cardium. No cultures of pericardium.
3 J. G.	4	4	Hydrothorax	Marked; rectal hem- orrhage. Epistaxis	Autopsy by Dr. Meierhof. Fine fibrinous exudate over part of pericardium. Microscopical a very few cells are seen, of small mononuclear type.	No cultures of pericardium.
4 C. L.	4	4	None.	Moderate; hemor- rhage in intestines and stomach; pete- chia on skin.	Autopsy by Dr. Mueller. Fresh fibrinous exudate. About 200 cc pericardial fluid. Abundant infiltration of small and large mononuclear cells, which ex- tended into muscle. Few scat- tered polys.	No cultures of pericardium.
5 D. V.	8	8	Pleurisy.	Moderate; rectal hemorrhage; pete- chia on skin.	Autopsy by Dr. Mackenzie. 150 to 200 cc rather dark, slightly turbid, amber fluid. Fresh granular fibrin. Microscopical numerous small mononuclear cells. Occasional poly.	No cultures of pericardium.
6 W. F.	(1)	..	Pleurisy.	Moderate; bleeding gums; epistaxis.	Autopsy by Dr. Mackenzie. 150 to 200 cc rather dark, slightly turbid, amber fluid. Fresh granular fibrin. Microscopical numerous small mononuclear cells. Occasional poly.	No cultures of pericardium.
7 C. A.	1	1	Hydrothorax.	Very slight.	No autopsy.	No cultures of pericardium.

<sup>1</sup> Diagnosis not made clinically.

8	M. E.	3	3	None.	None.	No autopsy.	Blood culture showed pneumococcus II. Pleural fluid also pneumococcus II. No cultures of pericardium.
9	T. L.	4	8	Marked; rectal hemorrhage; hematuria; epistaxis.	Marked; rectal hemorrhage; hematuria; epistaxis.	Autopsy by Dr. Stier. No fluid. Fine fibrinous adhesions. Muscle shows scattered areas of whitish color and smaller areas of darker red color, apparently hemorrhages. Microscopical fibrinous adhesions contain very few cells. Beneath them are numerous small mononuclear cells, with an occasional poly.	By Miss Cooper. Lung culture at autopsy sterile. No pericardial culture.
10	C. K.	13	13	Marked; epistaxis; hemorrhage from bladder and into skin.	Pleurisy.	Autopsy by Dr. Eggstein. Increased pericardial fluid. Firm white fibrinous masses in some places in others delicate fibrinous exudate. Microscopical loose fibrinous network, with only an occasional scattered small mononuclear.	No cultures.
11	A. K.	1	1	Slight; bleeding gums.	Hydrothorax.	No autopsy.	No cultures.
12	W. S.	9	1 yr. <sup>2</sup>	None.	Pleurisy.	Autopsy by Dr. Eggstein. Pericardium is adherent, and shows considerable mononuclear infiltration.	No cultures.
13	E. S.	5	5	Very marked; bleeding from gums, stomach, rectum, and vagina; epistaxis.	None.	No autopsy.	No cultures.
14	T. S.	3	5	None.	None.	No autopsy.	No cultures.
15	L. M.	16	16	Marked; hematemesis; epistaxis.	None.	Pericardial puncture. Clear amber fluid with fibrin shreds.	Pericardial fluid aspirated three hours after death sterile.
16	T. S.	(?)	..	None.	Hydrothorax.	No cells in smear; no autopsy. Autopsy by Dr. Meierhof. 100 cc of yellow turbid fluid. Fresh fibrinous adhesions between parietal and visceral pericardium. Microscopical fibrin tags are without cellular infiltration. Lymphocytes present beneath epicardium.	By Miss Frazier. Culture of lung at autopsy showed a pneumococcus II. Culture of pericardium was sterile, aerobically and anaerobically.

TABLE II.—PATHOLOGICAL AND BACTERIOLOGICAL DATA.—(Continued)

Cave.	Duration of rub, days.	Length of life after onset of rub, days.	Chest involvement.	Tendency to hemorrhage.	Pathology of pericardium.	Bacteriology.
17 H. W.	(4)	14	Pleurisy hydrothorax.	Moderate; epistaxis.	Autopsy by Dr. Evans. Pericardial fluid, dark red, 2000 cc. Fine fibrinous deposit. Pericardial hemorrhages over the pericardium. Microscopical small round cells present beneath the fibrin. (Tapped during life.)	By Miss Olmstead. Blood culture during life sterile. Blood culture at autopsy sterile. Smear or pericardial fluid obtained by tapping during life showed no organisms.
18 A. W.	7	7	None.	Moderate; petechiae; hemorrhages in conjunctiva; blood in colon irrigation.	Autopsy by Dr. Eggstein. Pericardium covered by many shaggy irregular fibrinous adhesions. These are bright red with a few areas of grayish mottling suggesting pus. In places fibrin 1 cm. thick. Microscopical exudate consists of polys, fibrin, red cells and masses of bacteria.	Autopsy culture of spleen and liver showed hemolytic staphylococcus aureus. Smear of heart showed many Gram-positive cocci, probably staphylococci.
19 R. A.	1	1	Pleurisy	None.	Autopsy by Dr. Mueller. Light fresh fibrinous exudate. Slight increase in fluid which is rather turbid. Fibrous layer of epicardium the seat of a moderate infiltration of polynuclear leukocytes and a few round cells.	By Miss Olmstead. Pericardial culture showed <i>B. coli</i> communis and staphylococcus albus. Gram-negative bacilli and Gram-positive coccus were seen on the smear.
20 M. G.	3	3	None.	Moderate; epistaxis; splitting up of blood.	Autopsy by Dr. Evans. Fine fibrinous exudate. No fluid. Epicardium distorted. It is edematous, infiltrated with plasma cells, polys, small round cells; and shows a fibrinous deposit.	By Miss Olmstead. Blood culture at autopsy sterile. No culture of pericardium.
21 L. L.	8	8	Pleurisy; hydrothorax.	Shown at autopsy; hemorrhages in brain, stomach and bladder.	Autopsy by Dr. Stillman. Brown turbid fluid, not in excess. Many flakes of fibrin over a dull pericardium. No cellular infiltration.	No pericardial culture.

\* Diagnosed by signs of effusion, fourteen days before death.

H. P.			Pleurisy.	None.	Autopsy by Dr. Pappenheimer. 100 cc pale yellow fluid. Large flakes and shreds of fibrin. Fresh adhesions; microscopical epicardium not seen.	No pericardial culture.
22		4				
23	L. J.	80	Pleurisy.	Moderate; epistaxis; coughed up blood.	Autopsy by Dr. MacCallum. 700 cc bloody fluid. Thickened pericardium. Soft fresh fi- brinous exudate. Pericardium is infiltrated moderately with mononuclear wandering cells and infrequent polys. Fibrin almost free from cells. Smear of pericardial fluid: pus, blood cells and Gram-positive cocci. No autopsy.	By Dr. Soper. Smear of pericar- dial fluid showed pus, blood- cells, and Gram-positive short- chained cocci. Culture was pure streptococcus.
24	R. T.	8 <sup>b</sup>	No autopsy; pleurisy.	Moderate; hematem- esis; epistaxis.	No autopsy.	No culture of pericardium.
25	E. S.	2	None.	None.	No autopsy.	No culture of pericardium.
26	B. G.	3	None.	None.	No autopsy.	No culture of pericardium.
27	E. H.	( <sup>c</sup> )	Pleurisy; hy- drothorax.	Slight; vomited clots of blood.	Autopsy by Dr. Evans. No ex- cess of fluid. Delicate fibrin- ous deposit. Small mononu- clears in epicardium.	No pericardial culture.
28	J. E.	20	Hydrothorax.	Slight; rectal hemor- rhage.	No autopsy. (Patient went home improved. Died three months later.)	No pericardial culture.
29	L. H.	4	None.	None.	No autopsy.	No pericardial culture.
30	V. F.	2	None.	Marked; purpura of skin and mucus membranes; bloody urine.	Autopsy by Dr. Allison. Thin fibrinous adhesions; 50 to 100 cc clear fluid. Leukocytic in- filtration, mostly mononu- clears, extending a short way into muscle.	By Miss Olmstead. Pericardial culture sterile.
Average		8	56 6 per cent.			

<sup>b</sup> Rub lasted eight days: Patient then left the hospital. Died three weeks later.

<sup>c</sup> Rub lasted twenty days and then disappeared. Patient left the hospital improved. Died three months after departure, four months after dis-  
appearance of rub.

<sup>d</sup> Diagnosis not made clinically.

The experimental production of acute pericarditis in animals by simulating the kidney damage in man has been productive largely of negative results. The ligature of both ureters or double nephrectomy is not followed by pericardial inflammation (Banti,<sup>43</sup> Keraval,<sup>41</sup> Beco,<sup>45</sup> Chatin and Guinard<sup>46</sup>). (One out of the five rabbits in Beco's series developed an acute serofibrinous pericarditis following ureter ligature. The pericardial fluid was sterile, but Beco admits the case is a bizarre one and does not prove the chemical theory.) Banti<sup>47</sup> also performed these experiments by first producing a point of lowered resistance through cauterization of the pericardial surface. An acute pericarditis develops which is more marked and of quicker onset than the control pericarditis that follows cauterization alone. This evidence, however, can hardly be accepted as proving anything definite. Keraval<sup>48</sup> injected urea and ammonium carbonate into the pericardial cavity without causing pericarditis. Chatin<sup>49</sup> found the serum of cases of "pericardite brightique" hypotoxic to animals rather than hypertoxic. These authors, because of the negative clinical bacteriology, nevertheless believed chemical irritation to be the main cause of pericarditis in chronic renal disease.

The observation of Flexner<sup>50</sup> upon terminal infections occurring in chronic diseases such as cirrhosis of the liver, diabetes mellitus and chronic nephritis shows that a local or general invasion by bacteria is frequently the immediate cause of death. Pericarditis, however, is especially characteristic as a complication of nephritis and not of other chronic affections. Although it may occur occasionally as a terminal infection in any chronic disease, there is an additional frequency in renal disease unexplained by the factors of infection.

Further evidence upon the etiology of this complication is of indirect nature. To determine whether the pericarditis had any relation to involvement of the other serous membranes, the incidence of involvement of the pleural cavity was tabulated in the cases that had pericarditis. Fibrinous pleurisy was present in 25 per cent, fibrinous pleurisy or hydrothorax in 56.6 per cent, peritonitis in none.

In the interest of the chemical theory an analogy may be drawn from the reactive pericarditis that follows infarction of heart muscle as after coronary closure. Here presumably a sterile chemical irritant derived from the products of muscle necrosis produces the pericarditis. Fischer<sup>51</sup> (1897) in fact explained the nephritic pericarditis upon very similar reasoning. He proposed that a myocarditis existed in uremia and that the irritant effect of the damaged muscle cells caused an inflammation in the adjoining serous layer of the pericardium. Rhomborg<sup>52</sup> has found in simple endocarditis thrombosis of the myocardial vessels and myocardial degeneration. Stengel<sup>53</sup> would couple this with what occurs in pericarditis, believing

that the symptoms of the latter are due to the underlying myocardial disease. Changes in the muscle fibers were observed in many of the cases of this series and occasionally mononuclear leukocytes were seen to invade the muscle nearby; but there was not enough of constancy either in location or character of the pathology to warrant any conclusions being drawn.

**Comment.** There are, then, two distinct theories that have been advanced to explain the etiology of this complication: (1) bacterial and (2) chemical. On the basis of the bacterial origin it may be stated that in a small group of cases microorganisms have been cultured from the inflamed pericardium. These organisms are of the same nature as those found by Flexner in the general and local infections of chronic renal disease. Furthermore the characteristic response to infection is shown by the presence of polynuclear leukocytes in the pericardium or pericardial fluid. This histology of the infected cases is demonstrated in the present series and in the infected cases reviewed in the literature. The evidence seems definite that in a small proportion of cases infection is the cause of the pericarditis.

In support of the chemical origin of the complication, the greatest argument is perhaps the existence of cases that have been found sterile after careful culture. Not only have aerobic and anaerobic cultures been made on very diverse media, but the pericardial fluid has been injected into animals, subcutaneously and intraperitoneally, with negative results. An additional important consideration is the non-infectious nature of the toxemia. The presence of a marked elevation in blood urea has been commented upon by French observers. Our results confirm the nitrogen retention and show in addition that there is simultaneously a notable acidosis and that both findings are present at the onset of the pericarditis. The secondary anemia was constantly present and generally severe. The tendency to hemorrhage was a conspicuous feature. As further evidence the differing pathological histology of the sterile group may be stressed. The pericardium of the sterile cases showed no infiltration with polynuclear leukocytes, but instead the presence of mononuclear leukocytes, or, infrequently, no cellular infiltration whatever. The remainder of the cases not cultured showed the pathological characteristics of the sterile group. This histology of the sterile group finds partial confirmation in the literature. In Chatin's carefully described case, mononuclear infiltration in the pericardium is fully noted; not so the cases from Banti's clinic, in which, however, the histology is incompletely given. The presence of round cells in an inflammatory area brings forth the possibility of a tuberculous etiology. Tuberculosis of the pericardium is not uncommon. However, this was not the pathology here. The mononuclear leukocytes were more likely to be scattered than localized; there were no tubercles, giant cells or characteristic granulation



tissue. The suggestion of a chemical irritant as cause of the majority of the cases is thus entirely compatible with the chemical nature of the toxemia and with the bacteriology and pathology of the condition. A clear-cut example of a pericarditis of non-infectious and therefore chemical origin is found in the acute pericarditis that follows infarction of heart muscle.

The possibility that both factors may have been present in an individual case presents itself. A pericardium previously inflamed, in response to a chemical agency, may finally become the seat of a terminal infection. For this reason sharp division of the cases may not always be possible. Case No. 23 may be mentioned as perhaps an example and the facts briefly outlined. In this case the pericardium showed a mononuclear infiltration, whereas the pericardial fluid contained pus and numerous cocci. The culture gave a pure streptococcus representing apparently a terminal infection. And yet the patient had had pericarditis for two and a half months before death. None of the other infected cases lived longer than seven days and the average was less than four days. Of the proved sterile cases, three were diagnosed and the average length of life after the onset of pericarditis was over ten days. The remainder of the cases fell pathologically into the sterile group and gave a considerably longer duration of life. The paucity of the proved cases and the complexity of the other findings limit the value of further comparisons.

**Summary.** 1. A description is given of the clinical and laboratory characteristics of a group of 30 cases of chronic nephritis at the time of development of an acute pericarditis. A marked nitrogen retention in the blood, a constantly present acidosis, a high blood-pressure, severe secondary anemia and a tendency to hemorrhage were conspicuous features.

2. It is pointed out that pericarditis is not a terminal complication in the sense that it always terminates the life of the patient. The average duration of life after the onset of the pericarditis was twenty-nine days. Excluding a patient that lived one year thereafter the average figure was sixteen days.

3. Death in many of these cases did not seem linked with an advancing heart failure or to the acidosis, but rather to the progressive retention of nitrogen in the blood.

4. Except in one case the diagnosis was made by the presence of pericardial friction and not by the signs of effusion. The diagnosis was made clinically in 90 per cent of the cases.

5. In 4 cases direct culture of the pericardium yielded pyogenic organisms. In 4 other cases culture of the pericardium was sterile. In the infected cases the cellular infiltration of the pericardium was predominantly of the polynuclear type; in the sterile cases the infiltration was predominantly of mononuclear type. The cases in which the pericardium was not cultured showed the pathological characteristics of the sterile group.

6. Reasons are given for believing that the majority of cases of pericarditis in chronic nephritis are of non-infectious origin. The assumption of a chemical irritant as cause of the complication is entirely compatible with the chemical toxemia of the patient and with the bacteriological and pathological findings in the pericardium.

7. A small group of cases exists in which frank infection of the pericardium is present. It is believed that the pericarditis in this group is generally of true infectious etiology. The possibility is present, however, that the complication may sometimes be of chemical origin and the inflamed pericardium become secondarily infected.

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## BILIARY TRACT DISEASE: SOME LESSONS LEARNED FROM DUODENOBILIARY DRAINAGE. FUTURE PROBLEMS. CITATION OF CASES.\*

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FOUR years have now elapsed since the late Professor Samuel J. Meltzer announced the effect that magnesium sulphate produced on the duodenum and on Oddi's sphincter of the common duct when locally introduced,<sup>1</sup> and four years have likewise elapsed since this

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observation of Meltzer's was applied clinically by means of the duodenal tube in the diagnosis, and, later, in the treatment of diseases of the biliary tract. Around this has gradually been built up a method of non-surgical drainage of the duodenobiliary tract which has already been proved to have great merit in diagnosis and is being proved to have a great field of usefulness in treatment. Much of the evolution of the technical details of this method have been published in earlier papers<sup>3, 4, 5, 6, 8, 12</sup>. A certain period of time must elapse before an estimate of this *method of treatment* can be properly made. During the past year a number of articles have been published which indicate that there is a general and widespread interest in this work. Brown<sup>9</sup> has favorably reported his results in a series of some 70 cases, the method being used principally for diagnosis. Einhorn<sup>13</sup> in a paper dealing with the action of various salts when introduced into the duodenum has attempted to put forward another explanation for the color changes following the installation of magnesium sulphate. In this article he has carefully noted the changes in the physical and clinical properties of the bile obtained, but we believe he has entirely misinterpreted their meaning. If Dr. Einhorn will follow our technic in detail or improve his own we feel convinced that as his personal experience with this method enlarges he will satisfy himself that our original premises are correct. Smithies<sup>14</sup> in a very complete paper has presented his favorable attitude toward the usefulness of this method of non-surgical drainage as an aid to both diagnosis and treatment. Recently, Whipple<sup>15</sup> has written on it from the surgical viewpoint and has emphasized its value as an aid to preoperative diagnosis. Also reference to this method can be found in chapters by Sir Humphrey Rolleston on gall-tract diseases which appear in the *Oxford Loose-leaf System of Medicine*.

Still more recently Simon<sup>16</sup> presented his experiences with this method, both diagnostically and therapeutically, and reports most favorably on it. His paper was thoroughly discussed and those familiar with the method appear to endorse it most strongly.

Finally, Crohn, Reiss and Radin<sup>17</sup> have presented the results of their investigations into the premises upon which the rationale of this method is based and have taken exception to some of the views we have expressed. We welcome the appearance of such a paper because it reflects a true investigative spirit and an attempt at a logical interpretation of the experimental data which they collected. Their contribution is too long to admit of free discussion in this paper and so important as to require a detailed reply which will be published elsewhere. They, however, conclude this paper as follows:

"While we have not succeeded in utilizing the diagnostic test of Lyon for the identification of chronic gall-bladder disease we think that the subject is entitled to much consideration and thought."

We believe that now sufficient water has run under the bridge to evaluate the position that this method of non-surgical biliary drainage occupies today and to further predicate our views as to certain possibilities it possesses for future endeavor. To this end we have undertaken an intensive study of 100 consecutive cases of gall-tract disease observed in private practice, starting from a period when the technique of this method had become perfected and carrying each case through a proper length of time so that it might be judged fairly on its own merits as an individual case.

The records of these patients were very carefully analyzed from 305 tabulated points of view, embracing etiology, symptomatology, physical examination of the entire gastro-intestinal tract and the common routine and various special methods of clinical examination. Thirty-one of them were studied by the roentgen ray and 35 of them by a careful review of the findings of previous abdominal laparotomies, 17 of which were operations or reoperations upon the biliary tract itself. These 17 laparotomies represented gall-tract operations done on 12 patients, 4 of whom had been operated upon twice and 1 patient three times, and all 12 of them were complaining bitterly of symptoms still referable to the upper right quadrant. Eight of these 100 cases we referred for operation or reoperation upon the gall tract and in each one our preoperative diagnostic findings were confirmed in detail. Twenty-two of them had had their appendices previously removed. Finally all were studied and restudied in the light of the direct evidence furnished by the cytology, chemistry and bacteriology of the bile and the manner of its delivery into the duodenum and by the reactions on the individual patient of this non-surgical method of biliary drainage. These various procedures provided the planks in the diagnostic platform. Ninety-four of these 100 cases were carried through a course of treatment by us and these cases particularly were critically analyzed and, where there was any reasonable doubt, the end-result was entered against us as being unsuccessful rather than successful.

We propose in this paper to point out some of the lessons we have learned in regard to the importance of securing certain historical, physical, laboratory and technical data as a necessity in properly diagnosing and classifying cases of gall-tract disease (with or without complications) as a first step in a decision for or against their management by surgical or non-surgical methods; to point out some of the lessons we have learned both for and against the therapeutic effectiveness of non-surgical biliary drainage; to point out some of our impressions both for and against the effectiveness of surgical procedures as exemplified in the cases studied, and, finally, to present some of our views as to future problems of biliary-tract disease which must be worked out.

In a critical study of the very excellent paper by Cheyney<sup>7</sup> on the "Diagnosis of Gall-bladder Disease" we were very much impressed

with the favorable case he (entirely unwittingly) made for the value of our method of studying the upper right quadrant group of patients by duodenobiliary drainage, as one of us has previously advocated. Any impartial reader of Cheyney's paper will probably realize that he has truly stated the facts in regard to his classification of his first three groups, based upon a diagnosis determinable alone upon a carefully taken history, physical examination amplified by the roentgen ray and the simpler routine laboratory studies of the stomach and the stools.

Permit us to quote from and comment on a paragraph from this paper. He says: "Thus in Group 1 of gall-bladder histories *recurring attacks of biliary colic* (italics are our own) characterize the story, with good health between. In Group 2 stomach symptoms play a prominent part but the *colic attacks* (italics are our own) still form the diagnostic feature. In Group 3 the stomach symptoms preponderate, *colic* (italics are our own) has disappeared and the gall-bladder symptoms have quieted down to minor importance."

*Comment.* These cases are all manifestly *late* cases in the sense of having already reached the formed calculus stage as demonstrated operatively in the finding of gall-stones in each of the illustrative cases Dr. Cheyney has selected or they are *late* cases in the association of formed pathology, such as thickened gall-bladder or duct walls, inflammatory adhesions or involvement of the pancreas, duodenum and their lymph nodes. *These are the easy gall-bladder cases to diagnose and they are easy because we diagnose them too late to accomplish anything except by surgical measures at some risk to the patient and often too late to permit the surgeon to apply corrective surgery which will be permanent in its good results for the patient.*

Cheyney further says, "In Group 4 there are no symptoms but those produced by the stomach, over months or years, and the gall-bladder speaks only vicariously, calling no attention directly to itself."

*Comment.* This is the important group to recognize in this stage of precalculous formation and prepathology. We must learn to diagnose this group if we desire to advance our present status of management of gall-bladder disease, and we can learn to do so by utilizing the intimate and direct diagnostic measures which have been emphasized in earlier papers and not wait for the months or years to pass during which stones are forming and inflammatory adhesions being developed. *Diagnosed at this stage many cures can be accomplished therapeutically by this method without having later recourse to surgery.*

Finally, Cheyney says: "There should really be a Group 5 described where the gall-bladder contains stones but gives rise to no symptoms of any kind until either some sudden attack of pain or operation performed for some other ailment reveals cholelithiasis.

But these cases sooner or later develop symptoms that put them into one of the four groups described, and they cannot be diagnosed until they do."

*Comment.* With this we would like to emphatically disagree. They can be diagnosed, but not by the analysis of the history or the physical examination, not by the forty-five minute test meal extraction nor by the roentgen-ray examination unless it is unequivocally positive. This group of so-called quiescent stones is necessarily also a late stage which has gone entirely unrecognized in its formative period, and we believe many cases of this group, as well as of Group 4, may in the future be included in the class of *preventive medicine* if more patients were routinely studied and treated by this method. Certainly all cases which give in their histories suggestive etiological factors such as typhoid fever, influenza, chronic bronchitis, tonsillitis recurrens, chronic nasopharyngitis, sinusitis or oral sepsis should have such a study made. Also those patients require such a study who give a history of catarrhal jaundice and also perhaps more particularly, those who have a progressive brownish pigmentation of the skin and who frequently show some jaundice of the sclera and of the hard palate or who may have the spider-web like tracings of capillary anastomoses of the collateral portal circulation just above the costal margin or who may have multiple telangiomas. This group of cases is too frequently overlooked and the skin pigmentation will be frequently found due to chronic poisoning from static bile within the gall-bladder or within the smaller bile ducts around the liver lobules or due to poisoning from the waste products filtered out from the portal circulation by the liver and excreted in the bile; but poisonous products which are again reabsorbed into the portal system and carried back to a liver whose cells are becoming more and more fatigued by the endless load thrown upon them until they ultimately fail to secrete a bile normal in its chemistry. Among this group will be found many cases of migraine, with or without biliousness, who have become victims of cholagogue laxative habits. Many cases of unsuspected duodenitis and of ileocolitis and sigmoiditis are among this group, as well as many cases whose appendices have been removed but who still continue to complain of gastro-intestinal dyspepsias of vague and nondescript types. Here, too, lie many cases of chronic visceroptosis with static bile from partial obstruction due to traction on supporting peritoneal attachments in the upper right quadrant. We believe that many of these types of cases may be like those found in Cheyney's fourth and fifth groups. Most of these cases *can* be diagnosed as having biliary tract disease, but only by an intimate study of the chemistry, physical properties and the cytology and bacteriology of the gastroduodenobiliary fluids when analyzed with and balanced against the evidence or data obtained by history and physical and laboratory examinations. It is not so difficult but that it may be mastered by any clinician who maintains a properly functioning workshop.

We trust that Dr. Cheyney will understand that the above comments are not intended in any sense as derogatory to him. His paper enhances his reputation as an able clinician. We feel that these comments are necessary to drive home the point of the great need of establishing earlier means of correctly diagnosing gall-tract disease, thereby giving us a better chance to throttle it in its infancy rather than in the old age of its life-cycle. This we firmly believe is possible by the careful and painstaking application of this method.

In our series of 100 consecutive gall-tract cases so studied we found 27 per cent of clean-cut gall-bladder syndromies, 4 per cent of gall-stone syndromies, 22 per cent of a mixed syndrome (gall tract, duodenum, appendix and colon), whereas 47 per cent presented only a vague atypical dyspepsia with or without biliousness. Eighty-eight per cent of these 47 cases showed an unsuspected masked infection of the duodenobiliary zone, among whom 50 per cent showed streptococcic infection. Of these 100 cases 32 of them could have been readily diagnosed as gall-tract disease if studied only in the light of the history and physical examination, supplemented by roentgen-ray examination and by our usual gastrointestinal methods; whereas 68 per cent of them would have failed of such diagnosis except by means of direct cytology, bacteriology and chemistry of the bile.

Here, then, is one lesson in diagnosis we have learned, and that the diagnoses were correct was proved by the subsequent results of the plan of treatment employed. It is not our purpose now to go into the minutiae of diagnosis which has been emphasized in previous papers, but rather to present the field of treatment by duodenobiliary drainage and some of the lessons it has taught us.

We rather take it for granted that most of you are aware of the inception and development of this method of more intimately approaching the diagnosis into diseases and disorders of the biliary tract and that you are now familiar with the possibilities of treating successfully by this non-surgical method of biliary-tract drainage many of the earlier and some of the later states of gall-bladder and duct disease.

Merely to refresh your memories let me recall to you that the fundamental basis of this method springs from the discovery of the late Professor Samuel J. Meltzer,<sup>1</sup> of the Rockefeller Institute, of the fact that a solution of magnesium sulphate when introduced locally into the duodenum will relax the tonus of the duodenal wall and the sphincter (Oddi's muscle) of the common bile duct, and that almost simultaneously with this relaxation the gall-bladder will expel its fluid contents, partially or wholly, into the duodenum. In previous papers one of us has pointed out the usual sequence of bile flow from the various components of the biliary system, and the method adopted for the recovery of this fluid for chemical, bacterio-



logical and cytological examinations relative to developing a new method of detailed diagnosis and as a direct check on the progress and efficiency of treatment.

It is now our privilege to come before this meeting and declare more positively our belief that it is now possible by this non-surgical method to drain the gall-bladder and biliary ducts of their fluid contents, within certain limits, to which attention has been called in previous papers. In the last of these papers thus far published the scope of this method was summed up as at present developed, first as a *means of diagnosis* of biliary diseases to supplement the usual clinical methods of diagnosis and help given us in many cases by the roentgenologist; secondly, as *an alternative method of treatment* of many types of gall-bladder and duct disease in which there arises a question of opinion as to whether surgery is or is not emphatically and immediately indicated; and, thirdly, as a *supplementary method* of postoperatively continuing the surgical principles of drainage in those cases incompletely cured by surgical means alone.

As a result of four years of practical application of this method of diagnosis and treatment of biliary-tract disease in a series of over 400 cases, we can most earnestly express our belief that it is now a proved and rational method in the successful treatment of early cases, and is possessed of great possibilities of future development in the prevention and control of many of the later and more severe states of disease of the biliary tract, and we trust it may hopefully be extended to certain diseases of the liver, of the pancreas and of some of the more serious of the problem diseases of internal medicine. Future papers will be devoted in part to a discussion of some of the results of an extension of this study into this larger field.

At this time we will not enter into a discussion of the principles and method of draining the gall-bladder except to have you refer briefly to this chart of the biliary system which hangs before you. We believe that the sphincter of Oddi normally is closed during the inter-digestive phase and that it opens in response to the stimulus of food chemistry. Then according to the law of contrary innervation propounded by Dr. Meltzer<sup>1</sup> the gall-bladder empties itself partially or wholly of its contents. The volume of bile expelled by the gall-bladder most probably depends upon the state and composition of gastric food chemistry reaching the duodenum if the experiments of Rost<sup>18</sup> are correct. It is by studying the departure from the normal physiological sequence of events, as seen to follow the local application of magnesium sulphate to the duodenum, as well as by a study of the gross and microscopic appearance, the bacteriology and the physiological chemistry of the recovered bile, that we arrive at definite conclusions relative to the state of the biliary apparatus, both as regards its physiology and pathology.

The first angle from which these cases were studied was from that

of previous operation. It was found that 35 cases had been abdominally operated on prior to the present study. Of these 12 had undergone gall-bladder surgery, 9 of them accompanied by appendectomy and 13 had had appendectomies independent of this gall-bladder surgery. After reviewing the 12 postoperative cases of gall-bladder surgery to determine residual infection it was found that positive bacteriology could be demonstrated in the biliary tract in 62 per cent of the cases in which a cholecystectomy had been done and in 100 per cent of the cases in which cholecystostomy had been practised. In this small series, then, it would seem that cholecystectomy is the operation of choice, considering only for the moment the question of residual infection. From the above it will be seen that surgery in the first place failed, in a too large percentage of cases, to free the biliary system of infection; and, in the second place, either failed to remove the primary focus causing multiple secondary foci or failed to recognize the early stages of biliary-tract infection and proceeded to remove the appendix alone.

The next point considered in our study was the question of attempting to find the primary source of the infection which had caused the gall-tract disease. We have felt for a long time that infection in the upper respiratory and digestive tracts is very frequently responsible for many of the acute or chronic conditions in the tract below. The six principal points of primary focal infection we found to be in the tonsils, gums or teeth, the posterior nares, sinuses or the bronchial tree. The five principal secondary foci are the stomach, the duodenum, the gall-bladder, the appendix and the rectosigmoid colon. These may be involved singly, all together, or in series, but surgical or medical treatment directed to any one of them alone will not preclude a recurrence or later development of trouble at one of the other sites unless the primary source of the infection is eradicated. Reviewing our operated group of patients from the standpoint of present or previous infection we found that in the 12 cases previously operated on we are able to demonstrate, by cultural methods, infection still present in the gall tract in 9 cases. Of the 12 cases we found that 10 of them, in addition, showed pathogenic focal infection in the tonsils, teeth or sinuses. Of the 4 other cases whose biliary tract had been previously been operated 1 of them was an exploratory cholecystotomy alone and 3 were for the release of gall-bladder adhesions alone. Here, of course, there was no surgical attempt to remove infection and therefore these cases must be excluded from this angle of analysis. Of 84 cases whose biliary tract had not been previously operated upon we could classify all of them as having various grades of cholecystitis, and that 24 of these 84 cases gave evidence by the tuning-fork or by roentgen-ray examination of the presence of adhesions. Lastly, 14 cases could be classified as having gall-stones in an active or quiescent stage. Analyzing our 84 cases

of non-operated gall-tract disease for residual focal infection we found 39 showed abscessed or suspiciously capped teeth; 29 cases had infected tonsils; 18 cases had pyorrhea; 17 cases had postnasal discharge, 3 of which were proved sinus infection; 6 cases had chronic bronchorrhea; and 4 cases had chronic otitis media. Several of these cases combined two or more points of infection.

We will not confuse you with figures relative to a discussion of the associated functional disturbances of the gastro-intestinal tract found in the series of patients, except to say that in the 14 cases of proved or probable cholelithiasis 57 per cent showed the gastric acidity by the fractional method either markedly reduced or absent and 21 per cent showed hyperacidity; but in those cases in which gall-stones could be reasonably excluded we found the gastric acidity reduced in only 34 per cent and absent in none, whereas 41 per cent in this group showed hyperacidity. In this respect our study confirms the findings of other investigators who have formulated a belief that a normal or increased acidity is a laboratory datum supporting a clinical assumption of cholecystitis as against cholelithiasis. This is in accord with the experimental evidence of Rost that the best normal physiological stimulus to the discharge of gall-bladder bile lies in a gastric chemistry rich in proteose, peptones and albumoses. Such conversion is only afforded by a normal or increased gastric juice. Therefore in the subacid or anacid gastric states the gall-bladder bile is more liable to become static and crystals are thrown out of solution. This is the potential stone or precalculous state. If mucosal inflammation or infection be added the formation of gall-stones is accelerated.

Analyzing the possibility of multiple infection of the gastro-intestinal tract we found that 22 patients who had previously had their appendix removed (9 of which were in conjunction with biliary-tract surgery) still showed evidence of residual infection of the gall tract; that 21 cases gave clinical evidence of appendicitis with proved infection of the gall-bladder; that 3 cases showed a lesion of the gall-bladder associated with duodenal ulcer; and that 4 cases suggested associated lesions of the gall-bladder, the duodenum and the appendix. A good many of these cases, also, had inflammation of the rectosigmoid, but were not specifically tabulated.

The question of the significance of biliary regurgitation into the fasting stomach is one that has always interested us and we have come to feel that *frank* biliary regurgitation is evidence of a disturbed physiology of the duodenobiliary mechanism. In the first place we believe the sphincter of Oddi should be closed except during the digestive cycle, and, in the second place, that reversed peristalsis should not occur normally in the fasting duodenum with certain exceptions not to be discussed here. In this study we found that of the cases with previous gall-bladder surgery 71 per cent showed both fasting and digesting biliary regurgitation as against

47 per cent of fasting and 23 per cent of digesting regurgitation in the non-operated cases. From this it would seem that operation on the gall-bladder very definitely disturbed the physiology of this segment of the gastro-intestinal tract. In addition it has been proved experimentally on animals, and by clinical experimental study of these postoperative gall-bladder cases, that surgery in each instance has destroyed the contrary innervation of the gall-bladder and Oddi's sphincter and has changed the normal physiologically intermittent discharge of bile into the duodenum into a pathologically continuous one, with, in many instances, harmful results, notably a severe and intractable diarrhea. All of this series of patients had complaints referable to the gastro-intestinal or biliary-tract systems, but, in addition to these localizing symptoms, a very large number (approximately 50 per cent) gave a history of symptoms suggesting focal infection or of autointoxication, the most prominent being easy fatigue, nausea, headache, dizziness and backache. In 54 of these 100 cases the physical findings in the upper right quadrant were entirely negative; in 46 definite tenderness, muscle spasm or rigidity could be demonstrated. There was no instance of palpable gall-bladder in the series. The average duration of ill health in these patients was eight years. Of this whole series positive bacteriology was demonstrated in 93 cases; the material obtained was sterile in 4 cases and no material was obtained in 3 cases. Of the 93 cases with positive bacteriology the streptococcic group was isolated in 50 per cent, staphylococci in 25 per cent, *Bacillus coli* in 15 per cent, *Bacillus subtilis* in 8 per cent, *Bacillus pyocyaneus* in 1 per cent and *Bacillus typhosus* in 1 per cent.

We would allude to one other fact brought out from our study, and that is the importance of recognizing catarrhal inflammatory or infected states of the duodenum, independent of duodenal ulcer or adhesions. These states are much more commonly present than is usually realized and have great significance in the causation of vague or atypical dyspepsias, and are conditions which often precede the later states of better developed pathology and a better understood symptom-complex. We found in our series of cases that 56 of them gave evidence of duodenitis, either simple catarrhal or with unusual exfoliation of duodenal epithelium, that 25 of these 56 cases gave evidence of bacterial infection of the duodenal mucosa and that 3 of them were infected with the *Lamblia* (or *Giardia*) intestinalis recoverable by tube in the living state. Obviously the diagnosis of these states of duodenitis can be made more accurately by the direct examination of the duodenal fluid than by any of the indirect methods.

To sum up the foregoing the final diagnosis in these 100 cases, based on a careful analysis of the history, physical examination, various special examinations and the detailed information derived from a diagnostic non-surgical biliary drainage, were divided as

follows: Gall-bladder syndromes, 27 per cent; gall-stone syndromes, 4 per cent; mixed syndrome (ulcer, appendix, gall-bladder), 22 per cent; and vague atypical dyspepsia (with or without biliousness), 47 per cent. There was "masked" infection, proved by culture, in 88 per cent of the cases. If, however, these cases had been studied only by the usual gastro-intestinal methods, supplemented by analysis of the history, physical examination and the roentgen ray, but without the added information derived from biliary drainage, only 32 per cent could have been diagnosed readily as gall-bladder cases. The remaining 68 per cent were impossible of such diagnosis except by means of direct cytology, bacteriology and chemistry of the bile.

To turn next to the question of treatment, 94 of these cases were treated by us. In all cases but one the chief therapeutic measure consisted in lavage and disinfection of the stomach followed by drainage of the biliary apparatus. The duodenum was then disinfected as a measure of local protection and a duodenal enema of Ringer's solution was given, reinforced where necessary with sodium sulphate, in order to secure a free fluid evacuation promptly and thus sweep out of the intestinal tract such infected bile as failed of recovery in our bottles. The duodenal enema of 250 cc is kept at 103° F. and allowed to drip in slowly in not less than twenty minutes. This whole procedure requires from two to three hours. Colonic irrigations were used only in exceptional cases where indicated. Rectosigmoidal insufflation, after Soper's methods gave us much better results.

As the individual necessities of each case demanded, other indirect therapeutic measures were combined with this direct topical treatment. Medicine was given by oral, subcutaneous, percutaneous and intravenous routes. The only oral medicines used were digestive substitution products and hepatic secretagogues. Electricity, dietetics, glandular therapy, hygiene, psychotherapy, exercise or rest were prescribed in certain cases.

But the first bulwark of treatment was our insistence on topical treatment of the stomach, duodenum, biliary tract and colon. The second agent in which we placed most reliance was the autogenous vaccines. Especially were these useful when they gave rise to a specific focalizing reaction reproducing one or more of the presenting symptoms, and those cases in which they occurred averaged better in their results. Among 58 cases receiving autogenous vaccines there were 17 who gave an unsolicited history of focalizing reactions simulating one or more of the chief complaints. Among these gall-bladder pain or soreness was mentioned 13 times and migraine was mentioned 5 times. Pain in a tooth socket following a vaccine of streptococci obtained from the gall-bladder and from the apex of a tooth root in 1 case. Pain in the tonsillar fossæ following a vaccine of streptococci from gall-bladder and tonsil in 1 case; soreness in

the appendiceal region was mentioned once; and increased joint involvement in a case presenting arthritis was mentioned once.

In summarizing the results of treatment by this method in this series of 94 patients we find that 73 of them showed complete arrest of symptoms (symptomatic recovery), 17 showed partial arrest of symptoms (improved) and that 4 of them were unimproved. But checking up from the objective standpoint, based upon a direct examination of the bile, we could demonstrate a complete return to normal findings in the bile in 47 cases, while 35 patients still showed abnormalities of the bile. On 12 patients there was insufficient data on this point to classify them, showing the need of correcting our errors of omission. As we were reviewing the results of treatment we noted the discrepancy in that 73 patients showed a complete symptomatic recovery, and yet in only 47 patients were we able to demonstrate a complete return to normal objective findings in the bile. This has indicated to us the inadequacy of considering simple arrest of symptoms as the criterion of a cure and emphasizes the need of continuing the treatment faithfully until the pathological findings disappear; otherwise relapse is extremely likely to occur. Again it was interesting to observe that as treatment was continued the complete improvement in findings ran more nearly parallel to the complete arrest of symptoms, and this, and this only, should be made the criterion of a real cure. Eight of these patients were diagnosed and treated non-surgically for a short period and then referred for operation, and were then again postoperatively treated by us. All of these patients, except one, made complete recoveries. Postoperative drainage, with protection of and treatment of the duodenum and intestinal tract, we believe to be a most important prophylactic measure to guard against relapse. Finally it was instructive to us to learn that of the 17 cases who complained of focalizing vaccine reactions 90 per cent had complete relief of their symptoms as against 77 per cent for the entire series; and, furthermore, 76 per cent showed complete return to normal findings against 50 per cent for the entire series. Hence our faith has grown in the efficiency of autogenous vaccines when properly selected by repeated culture checks, when properly prepared and properly administered, and particularly so when they give rise to focalizing reactions reproducing a presenting complaint.

In order to illustrate some of the lessons learned in the study of this series of patients, we will present briefly some of the case reports with a few words of comment.

Mr. F. S. W., aged thirty-seven years, was referred to us on June 9, 1920. With the exception of an attack of slight jaundice in 1900 and a tendency to recurrent tonsillitis prior to 1903, at which time his tonsils had been presumably removed by a tonsillotome operation,

this patient had enjoyed robust health until he suffered a severe attack of pandemic influenza in October, 1918. With this he was for five weeks very sick in bed. It was complicated by bronchopneumonia and cardiac insufficiency, which prolonged a slow convalescence through several months. In April, 1919, he had an attack of what was called "trench mouth," with spongy, bleeding gums, which lasted for one month. In March, 1920, he was told he had "acidosis," and had been given large doses of milk of magnesia, which he has continued to take for the past three months, with the result that his bowel movements have become very loose, contain slimy and shreddy mucus and are rather foul-smelling. In one year he had decreased in weight from 182 to 155 pounds, although he stands six feet two. His chief complaints were progressive weakness, a sense of nervous gripping in the right epigastrium, followed by a sense of "empty pain" about one hour after meals, sometimes wearing off spontaneously, but always made temporarily better by eating. He also complains of rectal tenesmus.

Physical examination disclosed numerous foci of infection as follows: The tonsils were inflamed and boggy, enlarged and cryptic, and pus could be readily expressed from both of them, smears from which recovered streptococci in abundance. Roentgen ray of his teeth showed three well-defined abscesses. His stomach examination disclosed a definite infective catarrhal gastritis, with a high normal secretion and motility retarded intermittently by pylorospasm. His duodenal cytology showed a moderate catarrhal and exfoliative duodenitis, and drainage of his gall-tract demonstrated a well-marked and exfoliative cholecystitis and choledochitis with masked infection. Cultures from his "B" bile recovered a hemolytic streptococcus. His gall-bladder discharge ranged between 90 and 150 c.c. of static, green-black, slightly turbid bile of increased viscosity, and contained large numbers of mucopus flocculations. The microscopy of this showed much bile-stained columnar epithelial exfoliation, numerous pus cells, a large amount of precipitated bile salts and cholesterin crystals and numerous colonies of bile-stained cocci. As a result of this inflammatory state we found the common duct uniformly open in the fasting state without the use of magnesium sulphate. This we believe to be evidence of disturbed physiology which may be functional or associated as a reflex to pylorospasm, appendicitis and colitis, but which occurs much more commonly when there is a duodenitis or inflammation of the gall tract.

He presented historically the symptom-complex of duodenal ulcer, but which, in the absence of specific laboratory and roentgen-ray confirmation, we have come to recognize as our mixed syndrome, which may be functional pylorospasm, duodenitis, duodenal ulcer, cholecystitis, appendicitis and, rarely, ileocolitis, with special involvement of the rectosigmoid. He gave, however, no direct clini-

cal, historical or physical findings that suggested gall-tract disease other than his attack of catarrhal jaundice twenty years previously. In addition, on examination we found a suspicious tenderness in the region of his appendix or cecum and an inflamed or spastic sigmoid. His blood showed a moderate secondary anemia with a negative Wassermann. His pulmonary, cardiac, renal and endocrine systems were relatively normal, but his nervous system was distinctly under tension, with a disturbed sleep picture of involuntary twitchings and a tendency to fantastic nightmares.

Here, then, was the picture of disseminated infection of the gastro-intestinal tract, most probably emanating from the tonsils and contributed to by the infection at his tooth roots, and, with his general resistance materially broken down by the severe type of influenza, with its complications, through which he had passed, we find his mucosal surfaces a fertile ground for the transplantation of the streptococcus.

As a first step in his treatment we had his tonsils removed and cultured and a vaccine was made from the hemolytic streptococci recovered from them, mixed in equal amount with the same organism grown from his gall-bladder bile. The similarity of growth of these streptococci in various media suggested them to be of the same strain. Two of the three teeth showing apical abscesses were extracted in Boston (no culture being made, unfortunately) and the sockets treated. He was then given a duodenobiliary drainage with a duodenal enema twice a week, together with a vaccine injection and iron citrate, sodium cacodylate and sodium glycerophosphate subcutaneously. His symptomatic response was prompt and his recovery was progressive. After seventeen such treatments he had gained fourteen pounds (from 155 to 169) and was called back to Boston by business and was referred into the care of Dr. Franklin W. White, who continued his treatment at greatly increased intervals. During our observation of him his abnormal findings in the duodenum and gall tract had progressively improved, and on December 31, 1920, Dr. White writes: "The last bile drainage was done on December 22. The bile was a very clear green-yellow with nothing abnormal in the sediment. He is feeling entirely well and has gained steadily from 169 to 186 pounds, which he weighs today." Six months later this patient still remains perfectly well.

*Comment.* This case represents a severe type of disseminated infection of the gastro-intestinal canal, with a masked lesion in the gall-bladder in the early stage, in which the symptoms are more suggestive of a pyloro-duodenal ulceration rather than involvement in the gall tract. It illustrates the importance of early diagnosis by the differential methods we have advocated. Later on the symptomatic picture will change and may call attention to the gall-bladder, but often by that time the pathology is extensive. This case finally teaches us that we may achieve excellent results



and may prevent the necessity for later surgery in many cases; but we must start our treatment by removing all recognizable foci higher up in the tract and then energetically treat the condition itself by topical and direct methods. We have 18 other cases in our series of 100 studied and treated who may be classed in this group.

Miss E. B., aged forty-three years, referred to us on July 11, 1920, had for ten years been suffering from severe prostrating migraine attacks which occurred in somewhat definite cycles every ten days to two weeks. She had tried out a great many remedies for relief of these sick headaches, with apparently no improvement.

She gave a history of absolutely no preceding infections in her past life except a stuffiness and catarrh in the left Eustachian tube, which has been under constant treatment by a most excellent specialist, with distinct improvement, and yet showed a tendency toward relapse.

On very careful physical examination she had absolutely normal findings in her eyes, nasopharynx, bronchial tree, lungs, heart, kidneys and pelvic organs. Her gastro-intestinal studies were likewise negative except for the particular findings in the gall-bladder and duodenum, which will be mentioned later. She had had constant and progressively more obstinate constipation for many years and represented a typical constipation-laxative habit vicious circle.

She states that the migraine attacks come almost without warning, with no causative factor to which she can ascribe them. They last from two to four days of intense prostrating "sick" attacks, and when at the worst are always accompanied by dry retching and terminal vomiting of bile, which usually brings the attack to a close. She has temporary relief in the use of cholagogues, especially calomel and salts. She describes the attacks as beginning with a "thick" feeling in the head, followed by pain which is first felt over the right eye and radiates down the temple to the right mastoid region. Less frequently the pain is felt, also, over the left orbital region, with the same distribution. This may be due to the influence of Arnold's auricular branch of the pneumogastric nerve. The abdominal physical findings were entirely negative, although special attention was paid to the gall-bladder region.

No direct diagnostic evidence could then be furnished from her examinations, which pointed toward the gall-bladder, except the historical data of recurring bilious attacks associated with migraine and the further fact that she had been noticing a progressive brownish pigmentation of her skin, which had been definitely deepening during recent years.

Her duodenobiliary drainage examinations supplied the necessary diagnostic data, for we found the gall-bladder bile to be static, ink-black, with increased viscosity and mucosity, and delivered inter-

mittently in the manner of the atonic flow previously described, and infected with a *Streptococcus viridans* and *Bacillus coli*. In this "B" bile was found a large amount of flocculent sediment, the cytology of which showed marked exfoliation of tall columnar, bile-stained gall-bladder epithelium, with much amorphous bile salts, cholesterin crystals, pus cells, spiraled strands of mucus and bile-stained bacteria in the colony formation representative of true infection.

Her treatment consisted of duodenobiliary drainage, followed by duodenal enema twice a week for two weeks, then once a week for a month, then twice a month for a period of three months. Autogenous vaccines were given every five to seven days and caused a focalizing reaction reproducing the migraine. With the exception of pancrobilin nothing else was used for her constipation.

The result of this treatment showed steady progressive improvement both in symptoms and in the objective findings in the bile. The migraine attacks became of lighter and lighter severity and of decreasing frequency, and she noted a general systemic improvement in her increased alertness, power of concentration, better sleep states, increased amount of vigor, and especially notable to her was the progressive absence of her sense of daytime drowsiness and the rather remarkable clearing of the brownish pigmentation of her skin and improvement in her complexion.

She has recently been seen and reexamined and has had no headache for a little over four months, and says she feels splendidly well. She had had no bilious attacks; her skin was clear and showed practically none of the earlier pigmentation; her bowels were moving once daily and naturally, without any laxation; and her biliary drainage showed an absence of all the direct evidence recorded above upon which her diagnosis had been based.

*(To be continued in February issue.)*

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## VISCERAL ADHESIONS AND BANDS; NORMAL INCIDENCE. A PRELIMINARY REPORT.<sup>1</sup>

BY JOHN BRYANT, M.D.,  
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THE material which is the basis of this paper was obtained before the World War incidental to a much more comprehensive investigation into the etiology and treatment of the chronic intestinal invalid.

<sup>1</sup> Read at the Annual Meeting of the Gastro-enterological Association, Boston, June 6, 1921. Original data for this article was obtained in 1912-1914 through the courtesy of Professors Pick and von Hanseman, of Berlin, Professor Fränkel of Hamburg and the students then working in their pathological institutes.

Its presentation has been delayed for several years, but there does not in the meantime appear to have been published any data which considers the question of visceral adhesions or bands from the same points of view.

The literature upon adhesions which is based upon reported facts is scanty, contradictory and inadequate. Although early writers frequently mentioned the existence of adhesions or bands within the abdomen, modern scientific literature upon the subject may be said to date from the exceedingly instructive paper by Virchow,<sup>2</sup> written in 1853. Virchow not only discussed the question of adhesions in the adult, but recognized that such abnormalities were occasionally found in the fetus, and referred to the fact that some of his contemporaries or predecessors had attributed these variations in the fetus to intra-uterine peritonitis. Since the time of Virchow, however, surprisingly little in the way of accurate data has been presented, the majority of recent writers having considered adhesions largely from a surgical point of view, and even then usually on the basis of personal opinion rather than of published facts.

One of the most valuable of such papers, from the surgical point of view, is that by Morris, in<sup>3</sup> which, although no actual data is given, he divides adhesions into four groups in the following order of frequency: (1) Gall-bladder, (2) cecum and appendix, (3) sigmoid and (4) pelvis. Robinson,<sup>4</sup> in 1896, reported observations based upon a variable number of cases, from 40 to 150, tending to show that the viscera most frequently involved were, in their order of frequency, the spleen, mesosigmoid, pelvis, cecum and appendix and gall-bladder. Opitz<sup>5</sup> reporting upon a series of 160 cases examined in 1914 agreed in general with Robinson, placing the sigmoid first in frequency, followed in order by the cecum and appendix.

There are also available a few studies of special areas, again mostly from a surgical point of view, of which by far the most reliable is the recent one by Smithies,<sup>6</sup> reporting on gall-bladder adhesions in a series of 1000 operative cases. In general, it may be said, however, that there has been practically no serious attempt made to study adhesions from the point of view of sex and progressive age or from the point of view of the normal occurrence of adhesions in unselected material.

It is believed that the present paper will to some extent supply this deficiency, since it is based upon a series of over 1000 observations upon 297 unselected consecutive postmortem cases of all ages and both sexes, the only cases excluded being those few recently postoperative or those exhibiting recent frank peritonitis.

<sup>2</sup> Virchow's Arch., 1853, 5, 281.

<sup>3</sup> Tr. Am. Assn. Obst. and Gynec., 1906, 19, 223.

<sup>4</sup> New York Med. Jour., 1896, 63, 101.

<sup>5</sup> Deutsch. Gesellsch. f. Chir., 1914, 43, 2, 107.

<sup>6</sup> Jour. Am. Med. Assn., 1918, 71, 1804.

In the obtaining of the original data, on the one hand every attempt was made to secure accuracy, the original notes on one case being written immediately after the completion of the examination and before proceeding to the examination of any subsequent case. On the other hand attempt was made not to overlook any variations from the accepted normal.

The data having been obtained they were next divided for purposes of study into male and female groups. After further study these groups were again subdivided into age periods as follows: fetal, birth to two years, two to ten years, every decade from ten to seventy years and a senile group composed of those cases seventy years of age or over. Although when thus subdivided the number of cases in each age group averaged only about 20, being from this point of view unsatisfactorily small, yet it was possible from this original subdivision to observe certain general tendencies which were largely substantiated by dividing the male and female groups into only four subgroups. These subgroups were: fetal, birth to forty years, forty years to senile and senile. At later stages of study these four groups were again frequently condensed into two, the group below forty years of age and the group above forty years of age.

It has been generally considered that where adhesions are found in the fetus, they are the exception and not the rule. This is not correct and even recent attention which has been given the question of developmental bands fails to take into consideration the extreme frequency with which such abnormal adhesions or bands occur within the fetal abdomen.

A careful study of the data available showed that there were only 8.9 per cent of 180 male cases of all ages in whom adhesions were absent; in other words, adhesions were present in 91.1 per cent of these 180 male cases. In this male group there was a total of 65 different adhesions or bands. Examination of the male fetal group showed that 100 per cent of 18 cases presented abnormalities; in other words, no male fetus was free from some form of abnormal adhesion or band.

In the female group of 117 cases of all ages there were but 14.5 per cent in whom adhesions were absent; in other words, adhesions were present in 85.5 per cent of these cases. In this female group there was a total variety of 57 different adhesions or bands. Examination of the female fetal group showed that adhesions were absent in only 12.5 per cent of 16 cases; in other words, adhesions were present in 87.5 per cent of these female fetal cases.

An examination of the total number of structures involved according to age showed that there was practically no increase above the fetal rate in either sex until the age of forty years. In the male fetus there was an average of 3.2 viscera per case involved; in the female fetal group the average involvement was 2.9 organs per case. The actual percentage increase above the fetal rate in the male

until the age of forty years was *nil*; in the female under the same conditions there was an increase of only 3.4 per cent above the fetal rate. This contrasts markedly with an increase of 43.8 per cent above the fetal rate for the number of structures involved in the males of over forty years of age and with an increased involvement under the same conditions in the female of 51.7 per cent.

The actual number of variations, in type of adhesions present in relation to the given age periods, shows a striking similarity to the figures just quoted, with the single exception that the sudden increase occurs in the thirty-year decade rather than in the forty-year decade. In other words, in both sexes below the age of thirty less than eleven different types of adhesions were found in any one age group in either sex, the number varying only one or two points from the fetal rate. Above the age of thirty, on the other hand, there is in both sexes a striking increase of almost 100 per cent in the variety of adhesions present, and this increased variety tends still further to increase up to and including the senile group.

The complexity of adhesions present, or, in other words, the number of structures involved in any given adhesive process, shows an interesting relation to age, and the general variation runs uniform in both sexes. There is from the fetus onward a progressive decrease in the number of simple adhesions present in any age group; on the other hand there is a progressive increase with increasing age in both sexes in the percentage of complex adhesions to be found in any given age group from fetal to senile.

The actual adhesions or bands present show a most interesting uniformity in both sexes not only in the fetus but in older ages as regards percentage frequency. The order of frequency in 297 cases of both sexes for the seven most frequent actual adhesions is shown in the Table.

ACTUAL ADHESIONS OR BANDS PRESENT. PERCENTAGE  
FREQUENCY, BOTH SEXES.

Adhesions or bands.	Male per cent.	Female per cent.
Gall-bladder to the duodenum and the transverse colon	25.6	24.8
Gall-bladder to the transverse colon . . . . .	17.2	9.4
Gall-bladder to the duodenum . . . . .	15.5	17.9
Appendix to the peritoneum . . . . .	15.0	5.9
Omentum to the ascending and the transverse colon .	11.1	12.0
Ascending colon to the transverse colon . . . . .	10.6	5.9
Duodenum to the peritoneum . . . . .	6.7	10.3

Study of the fetal groups shows that in both sexes the adhesion most frequently occurring is the same as that at the top of the list in the Table; in other words, from the gall-bladder to the duodenum and to the transverse colon. The second most frequent adhesion

in the fetus of both sexes is that of the gall-bladder to the transverse colon. It therefore seems reasonable to assert that these two most frequent adhesions are in both sexes of congenital or developmental origin, presumably existing as unabsorbed portions of the free edge of the lesser omentum or ligamentum hepaticocolicum.

A consideration of the location of adhesions from the point of view of the four quadrants of the abdomen shows that not only in the fetus but in all older age periods in both sexes the right upper quadrant is by far the most often involved. The right lower quadrant and then the left upper quadrant follow next in order of frequency.

A consideration of adhesions from the point of view of the individual organs involved at varying ages in both sexes is reserved for a later presentation.

**Conclusions.** 1. The frequency of occurrence of adhesions or bands in the fetus of both sexes has been greatly underestimated. Of a group of 34 fetal cases of both sexes only 5.9 per cent were free from demonstrable adhesions or bands; 100 per cent of the 18 male feti showed such variations from the normal.

2. The adhesions present in the fetus are less varied in number and of a definitely less complex type than those found to occur in later life.

3. The age of forty is critical in both sexes. There is practically no increase in frequency above the fetal rate of involvement for the different viscera by adhesions until the age of forty. Beyond the age of forty there is a sudden increase of about 50 per cent in the involvement of the different viscera by adhesions in both sexes, the increase being somewhat more marked in the female than in the male.

4. The two actual adhesions or bands found to occur most often in both sexes at all ages are in their order of frequency as follows: (a) Gall-bladder to the duodenum and to the transverse colon in both sexes; (b) gall-bladder to the transverse colon in the male and the gall-bladder to the duodenum in the female. In both the male and the females fetus the two adhesions or bands most frequently found were: (a) Gall-bladder to the duodenum and to the transverse colon; (b) gall-bladder to the transverse colon. It would therefore appear that these two most frequently occurring adhesions or bands are of congenital or developmental origin.

5. The regions or quadrants of the abdomen most frequently involved by adhesions or bands in both sexes are, in their order of frequency, as follows: Right upper quadrant, right lower quadrant, left upper quadrant, left lower quadrant.

## CERVICAL RIB, WITH A REPORT OF TWO CASES.

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THE detection of supernumerary rib in the living dates largely from the introduction of the roentgen ray into medicine. While in the lumbar region the diagnosis of an extra rib is only of academic interest, yet in the cervical region the subject becomes one of the utmost practical importance. According to Beck<sup>1</sup> the literature does not contain a single case in which the lumbar rib has caused any discomfort whatsoever, although, as pointed out by Kammerer<sup>2</sup> in 1901, "Supernumerary ribs are much more frequently found attached to lumbar than to cervical vertebræ." There is no consistent data regarding the frequency of cervical ribs. Fischel, of Prague, reports that in routine necropsy examinations, covering a period of four years, the condition was found in 1 per cent of all bodies examined. Gruber was able to demonstrate 45 cases on 76 bodies studied, while Henderson,<sup>3</sup> of the Mayo Clinic, states that of 80,000 patients examined only 31 cases of cervical rib were recorded. However, it is well to remember that only a few have any symptoms whatsoever, as is shown by the 139 cases analyzed by Pelling in 1894, in which only 3 patients had clinical symptoms.

The first description of the condition was made by Hunauld,<sup>4</sup> in 1742, but it was first recognized in life by Cooper in 1818, while the credit for the first successful removal on a living subject goes to Coote (1851). An article by Streissler, in 1913, is conceded to be one of the most exhaustive papers on the subject, there being 297 references with reports of 200 cases of cervical rib. However, Le Double's monumental work on *Variations of the Spine in Man*, published in 1912 and including 543 cases, deserves special mention.

Between 60 and 70 per cent of all reported cases of cervical rib have been in females. The condition in the majority of cases is bilateral, but the rib on one side is usually much longer than its fellow. In general, according to Beck, cervical rib is double in 67 per cent of cases and single in only 33 per cent, but a completely developed anomalous rib on both sides is regarded as quite rare, although occasionally they may reach to the sternum. The first case we have to report is bilateral and the second is unilateral, with a slight exostosis on the opposite side. The seventh cervical is by far the most frequent vertebra involved, although occasional cases

<sup>1</sup> Jour. Am. Med. Assn., June 17, 1905, 44, 1913.

<sup>2</sup> Ann. Surg., November, 1901, 34, 637.

<sup>3</sup> Mayo Clinics, 1913, p. 623.

<sup>4</sup> Church, A.: Jour. Am. Med. Assn., July 5, 1919, 73, 1.

have been reported of the sixth, fifth, fourth and third, and Jelliffe<sup>5</sup> also calls attention to cases reported by Thomas Murphy and Sherren, each having symptoms due to pressure on a cervical rib springing from the first cervical vertebra.

The exact cause of the formation of a cervical rib has never been given, although its embryological formation is clear. "Embryologically each cervical vertebra has a costal process which with the transverse process forms the costotransverse foramen. The cervical rib arises as a result of the abnormally great development of this costal process, which process is traceable on all the vertebræ and in the thoracic vertebra furnishes the normal ribs." (Henderson, Mayo Clinic.) Although the condition is a congenital one, rarely do the symptoms develop before the second decade. Several reasons have been advanced for this, although as yet there is no generally accepted explanation. Beck suggests that while trauma and such constitutional diseases as anemia, chlorosis, rheumatism, tuberculosis and scrofula apparently cause symptoms to appear; the loss of the fatty protective padding in these diseases is the actual causative agent. He states that "The tissues adapt themselves to the rib during the period of development and no discomfort arises where a certain amount of elasticity or yielding tendency of the tissues exist." Hirsch, in 1899, reported a case in which he believed the appearance of symptoms to be from a periostitis following direct trauma.

Gruber's classification is the one generally accepted and divides cervical rib into four classes, depending on their length:

1. A costal process increase not reaching beyond the transverse process. Cases under this group are not classed strictly as cervical ribs.

2. Extending beyond the transverse process, terminating in a free end or united to the first rib. The first case we have to report falls within this class.

3. A longer rib than in Class 2 and attached to the first rib by a ligament.

4. Complete ribs.

It has been repeatedly noticed that the symptoms produced are not definitely related to the size of the anomaly, as it is obviously the position and not the size that chiefly produces the symptoms. In general, the signs and symptoms may be divided into four divisions:

1. Hump-like prominence in the lateral cervical region.
2. The appearance of pressure symptoms, manifested by circulatory or nervous disturbances.
3. Superficial pulsations of the subclavian artery.
4. Cervical scoliosis.

<sup>5</sup> Jour. Am. Med. Assn., July 26, 1919, 73, 288.



In the majority of cases the rib is palpable in the neck, and on this alone the case is usually diagnosed and referred to the roentgenologist for confirmation, although Law<sup>6</sup> calls attention to the fact that the symptoms of an adventitious ligament may so closely simulate a cervical rib that only the roentgen ray can differentiate in the absence of operation.

Whenever the anterior extremity of the anomalous rib reaches far enough forward, the subclavian artery and brachial plexus pass over the rib, in which instance symptoms of compression may occur at any time. Pressure symptoms may therefore be referable to pressure on the brachial plexus, on the cervical sympathetic, the pneumogastric nerve or the subclavian artery. The most common and usually the first symptoms to appear are neuralgic pain in the neck, spreading to the head, thorax, arms and forearms, usually in the region innervated by the ulnar nerve and nerve of Wrisberg, as it is generally the inner cord which is first implicated. A common complaint is "rheumatism in the arm," many of the cases being diagnosed "brachial neuritis." On examination one may find formication and numbness in hands and fingers with some loss of muscle power in the entire extremity, although the reaction of degeneration apparently is never present. The temperature of the affected arm is usually lower than that of the sound side. Other symptoms which Kammerer and Planet both mention as rather frequently observed in their cases are the inability to fully extend the arm at the elbow and the occurrence of hoarseness attributable to pressure on the recurrent laryngeal nerve. Occasionally sensory changes appear early in the form of zones of anesthesia and paresthesia, although usually these changes make their appearance quite late. The circulatory disturbances are usually manifested by a feeling of numbness or tingling of the whole extremity, while frequently there can be detected an obvious atrophy of the thenar or hyperthenar group of muscles. Extreme circulatory disturbances may occur, as in a few cases reported in which gangrene of the fingers and hand occurred.

The elevation of the subclavian artery by the supernumerary rib results in a palpable pulsation which may cause suspicion of aneurysm. Occasionally true aneurysm does complicate the picture, but, as mentioned by Korg, there is always the danger in removing the anomalous rib so complicated, that one may hasten the growth of the aneurysm. He therefore advises strongly against its removal under these circumstances. The occasional aneurysmal dilatation of an artery distal to a point of partial constriction is due to the fact that below the constricted point there are definite changes in blood-pressure and in the structure of the vessel walls. These changes have been experimentally produced by Halsted<sup>7</sup> by partially constricting arteries with aluminum

<sup>6</sup> Ann. Surg., October, 1920, 72, 497.

<sup>7</sup> Surg., Gynec. and Obst., 1918, 27, 547.

bands. He found the systolic pressure reduced and the diastolic increased, thus lowering markedly the pulse pressure. Histologically, Halsted and Reid<sup>8</sup> have shown that there is a definite atrophy or partial disappearance of the elastic tissue in the walls for a short distance below the constriction, which probably plays an important part in causing the dilatation.

The fourth sign is cervical scoliosis, which is a rather rare type of scoliosis, but whenever found suggests the presence of cervical rib. Streissler in his study of 200 cases found this type of scoliosis in 16 per cent, and it is generally agreed that these two conditions frequently coexist.

According to Barker,<sup>9</sup> when there is a firm mass in the neck the differential diagnosis lies between:

1. Inflammatory enlargement.
2. A true tumor.
3. Enlargement of the salivary, thyroid or lymphatic glands.
4. Aneurysm.
5. Esophageal diverticulum.
6. Cervical rib.

Generally, careful physical examination is sufficient to make a tentative diagnosis of cervical rib, which can be definitely confirmed by the roentgen ray. However, Barker, reporting a cervical rib in his own case, calls attention to the association of syringomyelia with this anomaly. He states with pupillary disturbances, anesthesias or severe neuralgias it may be difficult to decide whether or not syringomyelia coexists. He speaks of his own case as showing a disassociation of cutaneous sensation, there being a loss of tactile and thermal but a retention of pain sense, while the syringomyelia type shows a loss of pain and thermal sense, with a retention of tactile sensation, and he suggests that the different types of anesthesia produced may be sufficient to determine whether the conditions coexist. The only other conditions of practical importance to be considered in the differential diagnosis are: (a) An adventitious ligament as reported by Law; (b) exostoses of the first rib, which may absolutely simulate cervical rib clinically, as was pointed out first by Mesnard in 1884; (c) Raynaud's disease, which Osler<sup>10</sup> divides into mild, moderate and severe types. The mild type, which may never go beyond an acrocyanosis on slight exposure, with sometimes swelling, throbbing and aching in the part affected, the hands more often than the feet may very easily be clinically mistaken for cervical rib, the roentgen ray being necessary for differentiation.

The treatment of cervical rib is divided generally into conservative and surgical. Rest in bed for a few weeks with elevation of

<sup>8</sup> Jour. Exper. Med. 1916, 24, 271, 287.

<sup>9</sup> Monographic Medicine, 4, 61.

<sup>10</sup> The Principles and Practice of Medicine, 1916, p 1121.

the arm and sometimes packs, massage, electricity, etc., is to be advised, to cause a subsidence of the acute symptoms, according to Ashhurst,<sup>11</sup> but most writers agree that if the congenital deformity causes any symptoms, conservative treatment is a waste of time, because here one has to deal with a disturbance placed in the way of normal blood and nerve paths which literally assumes the proportion of a foreign body if not removed. All surgeons are agreed in regarding its removal as an exceedingly difficult major operation, and all advise that the periosteum should be removed with the rib to prevent reformation.

The mode of approach varies. Some surgeons advise operation from the front, using either a transverse, oblique or vertical incision. This is the one usually used, dividing platysma and superficial fascia, doubly ligating and dividing the external jugular vein. After dividing the deep fascia and exposing the great vessels and brachial plexus, the vessels and nerves are cautiously retracted from over the cervical rib. The rib is separated from the soft parts, taking care to avoid injury, especially to the pleura, in removing the rib with bone forceps. If complete excision is very difficult, Binnie<sup>12</sup> states that occasionally it may be wise to resect only that portion of bone which is exercising injurious pressure on the vessels or nerves.

Others advise operation from behind as devised by Streissler and highly recommended by Roving<sup>13</sup> recently. A posterior longitudinal incision is made parallel to the spinous processes and about 2 cm. laterally from the midline. The trapezius, both rhomboids, serratus posticus and the splenius, are cut through and the fibers of the complexus and semispinalis are separated. A curved elevator is passed around the neck of the rib and the latter is divided. With this incision, however, the nerve to the serratus as it passes through the scalenus medius is in danger.

CASE I.—Female, aged twenty-four years, single, who entered St. Elizabeth's Hospital January 31, 1921, and was discharged, well, seventeen days later. The complaint was "numbness of the whole right arm." Family and past history were essentially negative.

*Present Illness.* Eight years ago the family physician called her attention to a hump-like prominence at the base of the neck on the right side. Soon after this the patient noticed that she had some numbness of the whole right arm and shoulder, but no other sensory disturbances were noticed. There has been no actual pain or paralysis at any time, although recently there has developed a definite paresis. Patient has had no trouble with her left arm. On physical examination her blood-pressure was found to be essen-

<sup>11</sup> *Surgery: Its Principles and Practice*, 2d Ed., 1920, p. 582

<sup>12</sup> *Operative Surgery*, 1916, p. 209.

<sup>13</sup> *Jour. Am. Med. Assn.*, July 26, 1919, 73, 376.

tially equal in both arms. The patient was a poorly nourished young woman, physical examination being apparently negative, with the exception of the partial obliteration of both supraclavicular fossæ, the right being practically obliterated. On pressure in the right supraclavicular fossa the patient complained of pain and numbness of the fingers and forearm on that side. The spine showed no scoliosis roentgen ray examination of the cervical spine showed the presence of two short cervical ribs, the right being longer than the left, and both arising from the seventh cervical vertebra. The laboratory report showed the blood and urine to be normal. Blood Wassermann was negative. At operation the right anomalous rib appeared to join the first rib just below the inner portion of the clavicle. It was exposed at this region with considerable difficulty and divided. It was also exposed posterior to the brachial plexus



CASE 1

and divided, and the section between these two points was removed. The segment which was removed consisted of a specimen of bone about one and three-eighths inches long, roughly resembling a metacarpal bone. Following this the brachial plexus and the subclavian vessels fell back in what would be their normal position. The wound was closed by suturing the superficial fascia and fat with a continuous suture of No. 00 tanned catgut and closing the skin with a subcuticular suture of silkworm gut.

The patient was placed in such a position that the head inclined toward the right shoulder and was kept in this position for twenty-four hours. Postoperative notes showed the patient had no motor or sensory disturbance and her recovery was uneventful.

*Diagnosis.* Bilateral cervical rib with pressure symptoms on the right side.

CASE II.—Female, aged twenty-one years, single, who entered St. Elizabeth's Hospital March 22, 1921, and was discharged well fifteen days later. The complaint was "blue and cold fingers of the right hand." Family history and past history were essentially negative.

*Present Illness.* Began about four months ago, when she noticed her forefinger, middle and little fingers turn white and the nails blue whenever she was exposed to cold. No pain at any time. Physical examination showed a hump-like prominence in the right supraclavicular fossa. Over the subclavian artery a distinct thrill and bruit were discovered. The hands and fingers were apparently normal except when one exerted pressure on the right subclavian



CASE 2

artery, at which time the fingers became pale and the finger-nails blue. The blood-pressure in both arms was essentially the same. Laboratory report showed the blood and urine to be normal. Blood Wassermann was negative. At operation the rib was exposed and divided with bone forceps, first at its anterior end, and as the distal portion of the rib was firmly attached to the first rib, it was necessary to remove the remainder piecemeal. The specimen consisted of four fragments of bone which measured in total about two and a half inches. The largest fragment was removed from immediately beneath the brachial plexus and subclavian artery. Recovery was uneventful.

*Diagnosis.* Right cervical rib with pressure symptoms. Exostosis on the left seventh cervical vertebra.

**Conclusions.** The pressure on the nerves and bloodvessels inducing pain, or even paresis of the arm, makes the subject one of surgical interest.

While the roentgen ray has been the means of confirming many tentative diagnoses of the anomaly, a comparison of clinical and necropsy statistics show that a large number escape detection. This is mainly because, as pointed out by Henderson, about 90 per cent of the cases are symptomless. Fischel in his necropsy findings reports the deformity in 1 per cent of cases, while Henderson states it was clinically recorded in only 31 of 80,000 patients examined at the Mayo Clinic.

The wide range in the variety and degree of symptoms which the patients present makes the diagnosis especially difficult, the one almost pathognomonic sign being a pulsating mass above the clavicle, which Cabot<sup>14</sup> states means cervical rib in nine cases out of ten.

Conservative treatment in some cases has been of value, and apparently even a few cases have been cured by it; but for the reasons stated, whenever signs of compression occur no operation is indicated.

Acknowledgment is made to Dr. J. Shelton Horsley for his permission to report these cases, which occurred on his service.

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## SKIN TESTS WITH FOREIGN PROTEINS IN VARIOUS CONDITIONS.<sup>1</sup>

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Skin tests with foreign proteins are today being used by numerous investigators and physicians in the study of a large variety of diseases in the hope of identifying a sensitiveness to some foreign protein which may subsequently be shown to be the cause of the symptoms in that patient. This method of diagnosis is being used not only in asthma, hay fever and urticaria, certain cases of which are clearly dependent upon an underlying "asthmatic state," but also in many other conditions in which there is little evidence that hypersensitiveness plays a definite part, but in most of which the symptoms are essentially chronic.

In asthma, hay fever and urticaria, in which so many cases are clearly due to foreign proteins, it is reasonable to suppose for them a

<sup>14</sup> Differential Diagnosis, 1915, p. 338.

<sup>1</sup> From the Anaphylaxis Clinic of the Massachusetts General Hospital.

basis for this sensitiveness which we may call the "asthmatic state," which, in so far as the reactions to the specific protein either by ingestion or injection are immediate and severe, is akin to the experimental anaphylaxis in animals.

The nature of this "asthmatic state" is unknown, but its presence perhaps explains why the symptoms due to foreign protein absorption may result in one patient in urticaria while in another patient they result in chronic headache or chronic indigestion, etc. The present paper is an attempt to review recent literature on this subject and to present the results of my own studies.

In a recent publication<sup>2</sup> an attempt was made to classify cases of asthma and allied conditions. In describing the results of skin tests in asthmatics, attention has been paid to this classification.

Skin tests have been known since 1873. At that time Blackley<sup>3</sup> noted that the installation of crude pollen into the eyes of hay fever patients produced swelling of the mucous membrane. In a later experiment he found that pollen grains when rubbed into a break in the skin produced a local reaction, and he likewise found that a decoction of the pollen could in certain instances produce the same result. Dunbar,<sup>4</sup> in 1903, demonstrated that this local reaction was not due to the mechanical structure of the pollen granules, since it could be obtained by an alcoholic or saline extract of the pollen.

In 1905 von Pirquet and Schick<sup>5</sup> in their classical description of serum disease noted that a reinjection of horse serum causes an intensive edema around the point of injection. Such a development of sensitiveness following artificial sensitization has been shown to occur after an incubation period of seven to ten days and to follow the appearance of the serum disease itself.

In 1912 Schloss<sup>6</sup> described skin tests by the von Pirquet technic to egg-white, and demonstrated that the various chemical fractions of egg-white could each one produce a reaction. He also described skin tests to nuts and to oatmeal.

In 1914 Goodale<sup>7</sup> demonstrated that when a drop of horse serum was placed into a superficial cut in the skin of patients suffering from horse asthma, a local reaction appeared, and also that a drop of the same horse serum placed on the anterior turbinate caused violent sneezing with typical symptoms of horse asthma. A little later he studied hay fever, and found local skin reactions to dilute

<sup>2</sup> Rackemann, F. M.: A Clinical Classification of Asthma. (See *AM. JOUR. MED. SCI.*, December, 1921, 162, 802.)

<sup>3</sup> Experimental Researches on the Cause and Nature of Hay Fever, London, 1873.

<sup>4</sup> Hay Fever, *Journal of Hygiene*, 1903, 13, 105.

<sup>5</sup> Die Serumkrankheit, Leipzig, 1905.

<sup>6</sup> A Case of Allergy to Common Foods, *Am. Jour. Dis. Children*, 1912, 14, 341.

<sup>7</sup> Skin Reactions in Anaphylaxis, *British Med. and Surg. Jour.*, 1914, 171, 695.

alcoholic extracts of those plant pollens which corresponded accurately to the dates of onset and subsidence of the hay fever. Talbot,<sup>8</sup> in 1914, studied infants by testing their skin with egg-white and found that in all cases in which egg caused indigestion there was a violent skin test to the protein.

In recent years the literature has remarkably increased to its present considerable size. Positive skin tests do not occur in normal individuals, and when they do occur in those who are apparently normal, there is always a reason, although in many cases no satisfactory explanation can be given. Schloss<sup>9</sup> has recently shown that a positive skin test indicates that the patient is sensitive to that protein, but there are undoubtedly differences in the behavior of adults and children in this respect. In 1916 Talbot<sup>10</sup> performed skin tests with egg-white as a routine on every admission to his ward and found 3 positives out of 85 tests. No further studies in the 3 were made. Throughout the literature are many notes of positive tests in adults for which there is no explanation. In the present study, skin tests with a variety of at least 15 different proteins were done with negative results in a total of over 600 patients, in most of whom sensitiveness to proteins was a reasonable and probable explanation of the symptoms. The results of skin tests performed by other observers are rather difficult of analysis chiefly because of the fact that the proteins used are differently prepared and that the methods of application are also different.

Walker has probably done as much in this field as anyone. In 1918 his study of 400 patients with asthma<sup>11</sup> showed that 48 per cent gave positive tests, but of the 130 patients below the age of twenty-five years, 64.5 per cent were positive and of those below the age of fifteen years, 69.1 per cent were positive. These tests were made by the same technic as the writer's.

A large series of 800 tests has recently been reported from the Mayo Clinic by Sanford,<sup>12</sup> who, using Walker's technic, found over 25 per cent of the cases positive; no attempt at grouping these patients was made.

Gottlieb<sup>13</sup> did skin tests with a large number of test substances in 32 patients, finding one or more positive results in 23. Sterling<sup>14</sup> found only 1 positive in a series of 12 asthmatics tested. Skin tests in dermatology have been recently shown to be of some import-

<sup>8</sup> Asthma in Children, Boston Med. and Surg. Jour., 1914, **171**, 708.

<sup>9</sup> Loc. cit.

<sup>10</sup> Asthma in Children, II, Boston Med. and Surg. Jour., 1916, **175**, 191.

<sup>11</sup> Walker, I. C.: Clinical Study of 400 Patients with Bronchial Asthma, Boston Med. and Surg. Jour., 1918, **179**, 288.

<sup>12</sup> Protein Sensitization in Asthma and Hay Fever, Jour. Am. Med. Assn., 1920, **74**, 124.

<sup>13</sup> Results of Tests in Hay Fever and Asthma, Jour. Am. Med. Assn., 1920, **75**, 814.

<sup>14</sup> Results of Tests for Food Protein Sensitiveness in Small Group of Asthmatics, Pennsylvania Med. Jour., 1918, **22**, 135.



ance. In 1916 Strickler and Goldberg,<sup>15</sup> using purified alkaline salt solution extracts of various foodstuffs, found 11 positive reactions in testing 29 cases of various dermatoses. Their work, however, has been supplanted by the careful studies of Schloss,<sup>16</sup> whose results are as follows: Urticaria, angioneurotic edema and erythema multiforme, 19 positives in 72 patients (26.3 per cent); eczema under sixteen months, 53 cases with 40 cases (77.4 per cent) giving positive reactions; eczema over sixteen months, 24 cases with 10 positive tests (41.6 per cent). O'Keefe<sup>17</sup> studied the skin tests in 70 cases of infantile eczema and found that 29, or 41 per cent of these patients, gave a positive reaction to one or more foods, egg-white being the commonest offender.

While, then, positive tests are always important, negative tests are by no means of equal importance, as has been recently brought out by Schloss,<sup>18</sup> who has observed that in a sensitive individual cutaneous tests may become negative because of a temporary desensitization.

The cases reported in the present work are only those in whom a relatively large number of tests have been done, so that in the case, for example, of hay fever the number appears small. There are two methods of testing the skin: (1) The cutaneous method, by which a small quantity of dry protein powder is mixed *in situ* on the arm with a diluent and a scratch made through the resulting solution; positive reactions appear within fifteen to twenty minutes and last for about two hours. (2) The intradermal method by which a measured quantity of sterile protein solution in known concentration is injected between the layers of the skin. Tests by the intradermal method appear within five to fifteen minutes and disappear in about one hour. They are very delicate and in the author's hand have been found accurate and easy of interpretation. Indeed, in several cases in which it was of the utmost importance to determine accurately whether certain seasonal symptoms were due to hay fever or not, the cutaneous (scratch) tests to ragweed and timothy pollen in a strong (1 to 100) dilution were negative, whereas the intradermal method using these two pollens in a weaker (1 to 1000) dilution demonstrated a definite sensitiveness to pollen.

On this point Walker<sup>19</sup> concludes, after some study, that the intradermal is less specific and is too sensitive. There is, of course, no question that the intradermal method is more difficult of application, since in the first place a chemically as well as a bacteriologically clean syringe and needle are required for each test, and in

<sup>15</sup> Anaphylactic Food Reactions in Dermatology, Jour. Am. Med. Assn., 1916, 66, 249.

<sup>16</sup> Allergy in Infants and Children, Am. Jour. Dis. Children 1920, 19, 433.

<sup>17</sup> Dietetic Infantile Eczema, Boston Med. and Surg. Jour., 1920, 183, 569.

<sup>18</sup> Loc. cit.

<sup>19</sup> Comparison between Cutaneous and Intradermal Skin Tests, Jour. Med. Research, 1917, 37, 287.

the second place the proteins used must be in a sterile solution which produces absolutely no reaction when injected into normal persons. This method is delicate. In the interpretation of any of these tests it is important not to read as positive, reactions above any certain size, but rather to read the test according to their relative sizes and to compare them directly one with another and with the control test. The typical positive test by either method should consist of an urticarial wheal having a sharply defined irregular border; it is usually pale in color but is surrounded by a zone of bright erythema. All tests by all methods should give entirely negative reactions in normal individuals.

The present study is based upon skin tests done by the cutaneous method, using the proteins in some of the common foods as well as in the animal dusts and danders.<sup>20</sup> Only those cases are reported in which at least fifteen different test substances were used, though in most of the cases from twenty to thirty tests were employed.

The list of test substances includes:

Wheat protease	Horse-hair	Casein	Timothy
Wheat leucosin	Cat-hair	Cow's milk	Bean
Buckwheat	Dog-hair	Beef	Pea
Rye	Goose feathers	Pork	Lima beans
Barley	Chicken feathers	Chicken	Potato
Oat	Sheep wool	Lamb	Peanut
Rice	Egg-white	Codfish	Strawberry
Corn	Egg-yolk	Mackerel	Wheat globulin
Horst dander	Lactalbumen	Ragweed	Wheat.
Orris powder			

In certain cases, and in addition to the cutaneous tests, the intradermal method with solutions of the pollens, of egg-white or of horse-hair extract was used for corroboration in case a corresponding sensitiveness was expected from the history.

**Hay Fever and Pollen Asthma.** When the symptoms of hay fever occur only during the pollen season, tests to foods, etc., are not ordinarily indicated. Such tests were done in 118 cases, all of which had, of course, a positive test to one or more pollens and in most of which the history vaguely suggested a possible susceptibility to foods, horses, etc. It was found that in 48 instances, or about 40 per cent of these patients, there was a positive test to some protein other than the pollens.

#### TESTS IN HAY FEVER SHOWING THE NUMBER OF CASES IN WHICH TESTS TO FOODS, DUSTS, ETC., WERE POSITIVE.

	Total tests.	Number positive.	Per cent positive.
Late hay fever . . . . .	24	11	45.8
Early hay fever . . . . .	19	5	26.3
Double hay fever . . . . .	16	9	56.2
Pollen asthma . . . . .	37	14	38
Complicated pollen asthma . . . . .	22	9	41
	<hr/> 118	<hr/> 48	<hr/> 40.6

<sup>20</sup> The proteins used were obtained from the Arlington Chemical Company.

It is noteworthy that the proportion of other positive tests was greater in adults than in children with pollen sensitiveness.

If we analyze these positive cases we find that in the adults the cereals gave positive tests in 16 cases, and in each case the food was withdrawn from the diet, but in none of these cases can it be said that this withdrawal produced any good result; and in none of the cases was the patient aware of the sensitiveness before the tests were made.

Animal dusts gave positive tests in 11 adults, and here the story is different because in 6 of these patients withdrawal of feather pillows consequent upon the positive test to goose feathers, brought about a definite improvement in the symptoms. In 2 adults positive tests were obtained to each protein in the dust group, namely: horse, cat, dog and feathers, but only 1 patient (R. J.) knew that she could not go near cats without trouble.

In children with hay fever there were only 6 cases in which a positive test to foods was obtained, although such tests were performed in 21 cases of the 51 children suffering from pollen sensitiveness.

**Horse Asthma.** There were 45 cases of horse asthma of all ages—a diagnosis made only in case the positive test to horse dander or to horse-hair extract<sup>21</sup> or to both was substantiated by the patient's knowledge of susceptibility to horses or by the fact that his asthma was associated with certain places in which animals were in evidence. In 15 cases of horse asthma, tests with other proteins showed positive results as follows: Wheat proteose in 1 case, wheat leucosin in 2 cases, cat-hair in 5, dog-hair in 4, goose feathers in 3 and ragweed, timothy and pea in 2 each, and egg-white, egg-yolk and beef in 1 each. Avoidance of the corresponding proteins was advised in each case.

**Dust Asthma.** In addition to cases of horse asthma there is a group of 31 patients with "dust asthma" in which group is included those cases with sensitiveness not only to animal dusts as feathers, cat and dog hair, but also to other substances existing in dust, as wheat flour, orris powder, etc. This subgroup of asthma is so complicated and at the same time so important that it has seemed best to tabulate the results as found in the 17 adults and 1 child. (See Chart I.) Thirteen patients are not tabulated since only a very few tests were done and yet the asthma in each was definitely associated with some particular occupation or environment: a coffee worker gave a very fair test to coffee dust.

A study of Chart I shows that 6 adults and 1 child were sensitive to feathers, a fact corroborated by the relief to their asthma following the removal of feather-pillows. But although each patient is sensitive to feathers, yet there are many other positive

<sup>21</sup> These two terms "Horse Dander" and "Horse Hair Extract" refer to two different preparations used in the tests.

CHART I. DUST ASTHMA. ADULTS AND CHILDREN. 18 CASES. SKIN TESTS TO FOREIGN PROTEINS IN.

Number.	Initials.	Age.	Family history.	Wheat protease.	Wheat Leucosin.	Buckwheat.	Rye.	Barley.	Oat.	Rice.	Corn.	Horse dander.	Horse-hair.	Cat hair.	Dog hair.	Goose feathers.	Chicken feathers.	Sheep wool.	Egg white.	Egg yolk.	Lactalbumen.	Casein.	Cow's milk.	Beef.	Pork.	Chicken.	Lamb.	Codfish.	Maccherel.	Ragweed.	Timothy.	Beet.	Bean.	Pea.	Lima bean.	Potato.	Peanut.	Wheat globulin.	Wheat.						
Feathers																																													
1, SMG		12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
2, JJS		35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
3, KG		39	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
4, WE		32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
5, HB		22	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
6, EW		37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
7, ADP		19	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Wheat			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
8, AP		58	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
9, MM		38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
10, WL		16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
11, AK		40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
12, MB		26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
13, FA		..	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Unknown			0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14, CH		27	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
15, WR		26	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
16, KN		34	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
17, SC		30	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
18, LW		21	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

tests. Indeed, all but one of these patients react to at least three other proteins besides feathers. In Cases 3 and 4 with definite sensitiveness to wheat, bread and cereals were also removed from the diet, but were subsequently added again without increasing the symptoms. Eight patients, including 2 not charted, were sensitive to the wheat proteins and each gave a history of asthma aggravated by contact with flour dust such as in making bread. Five of these 8 were professional bakers, the other 3 being housewives. In this wheat group there were positive tests not only to other cereals but to odd proteins, such as pea, potato and lamb, the significance of which is unknown.

This sensitiveness to a number of different proteins—multiple sensitiveness—may be particularly marked, a fact which often adds to the difficulty of correct diagnosis. For example, the findings in 5 other patients are added to Chart I. In these 5 patients asthma was worse under certain fairly definite circumstances not adequately explained by the positive tests obtained.

Thus it is apparent that the finding of a positive test does not always explain the actual cause of symptoms. In other words, to be conclusive, positive tests must be confirmed by the patient's history or must be controlled by subsequent clinical experiments. It is, of course, self-evident that thoroughly complete tests would be almost impossible of performance because of the unlimited number of possibilities, so that the causative proteins might easily have been overlooked.

**Food Asthma.** In only 19, or 3 per cent, of the 648 cases of asthma were proteins in food considered to be the cause of symptoms. As in the case of dust asthma, so here positive tests were invariably found to be multiple and in most cases not confined to one protein group. With the help of the history as well as by clinical experiment it was determined that the asthma in these cases was due in 10 cases to egg, in 4 to wheat, in 2 to meat and in 1 each to nuts, fish and milk. In 4 others the positive tests were so numerous and complicated that no one food could be held responsible.

**Bacterial Asthma.** In the present series a diagnosis of bacterial asthma (including perennial asthma) was made in 156 patients, and of these about 100 had fairly complete skin tests. Out of 103 patients tested 22 showed positive reactions. An analysis of the results obtained in these cases shows that positive tests to only one protein were obtained in only 3 cases, while 1 other patient had only two positive tests. Two other patients had a number of different positive tests but all to substances in one protein group. The diagnosis of bacterial asthma was made in these last 2 cases largely by exclusion, as it was subsequently established that avoidance of the particular group of proteins did not bring relief to the symptoms. In other cases positive tests were scattered throughout the protein groups. One of these cases of bacterial asthma gave beautiful tests

to the wheat proteins and to barley, rye and oats; but when it was discovered that he was a diabetic, and in recent years had rarely if ever eaten wheat or cereals of any sort, and when all chances of his exposure to cereals and grain dust had been excluded, the absurdity of the test finding in this particular case was evident.

**Emphysema.** In the cases of emphysema skin tests were done in 133 cases, but in only 34 were positive results obtained. This latter figure includes 13 cases of emphysema on a background of pollen asthma and 8 cases on a background of animal dust asthma. Here, again, positive results were found to be well distributed throughout the various protein groups and were confined to one group in only 3 cases. Except for the 21 cases whose emphysema could be shown by history, skin tests and reaction to treatment to be due to foreign proteins, no one of the other 13 patients with positive tests gave any history of sensitiveness to proteins.

Six of these 13 patients were found to be sensitive to one or more of the cereal proteins, and were told to avoid all bread and cereals, but it is difficult to know how much this advice has helped them, especially as in certain cases they have, after a trial of from three weeks to six months, gone back to bread without change in their asthma or emphysema. In a previous publication<sup>22</sup> the relation of emphysema to other forms of asthma was discussed, and in consequence of the findings there it is evident that in the presence of organic changes in the lungs, little in the way of protein treatment can be accomplished.

In this series, skin tests were done in 78 cases of reflex asthma and in 35 cases of "unclassified asthma," but in only 7 of these 113 cases were the results positive.

**Other Conditions Allied to Asthma and Hay Fever.** In addition to the work on asthma, many patients with other conditions have been tested. Chief among these conditions is vasomotor rhinitis, in which the physical findings in the nose are quite the same as those during the acute hay fever attack. As here used the term refers to a perennial condition which runs on from day to day and from week to week regardless of the environment or occupation of the patient and without any apparent cause for its changes in severity. The cases already described under hay fever, horse asthma and dust asthma are not included.

One hundred and ninety-eight patients with this ailment were tested and studied in some detail. Forty-five, or 22.7 per cent, were found to give positive skin tests. These positive skin tests were confined to one group of proteins in about half of the cases. Although only a few of these patients were heard from after the tests were done, these few were practically all much relieved by the advice to avoid the protein giving the test. Thirteen were sensitive to

<sup>22</sup> Rackemann, F. M.: A Clinical Classification of Asthma. (See AM. JOUR. MED. SCI., December, 1921, 162, 802.)

orris powder and here the advice to give up its use was often striking. In several cases, the importance of further study is well illustrated: For example: M. G. was a patient whose tests by the cutaneous method were entirely negative and who had been treated with ten doses of a vaccine made from her nasal secretion without result. Finally, the intradermal method revealed a slightly positive test to horse-hair extract, and treatment with this has to date caused a definite improvement.

Five patients were advised to give up their feather pillows, with the result that their symptoms were very much relieved.

Five patients in whom the results were not good, all gave reactions to one or more of the cereal group, but whether their attention to instructions was perfect or not the fact remains that the advice to avoid bread and all wheat was not followed by any definite clinical improvement. The same general experience is true of the other patients with vasomotor rhinitis who gave positive tests in more than one protein group. The large majority of these tests were in the animal hair group, but avoidance of feather pillows was not of any striking benefit. Unfortunately in none of these other patients was treatment with horse-hair carried out. On the other hand 2 of these patients were sensitive to ragweed, and treatment with ragweed extract during the summer seemed to have a definite and permanent good effect upon their condition in spite of the perennial character.

From the above it is perhaps reasonable to conclude that in vasomotor rhinitis the responsible proteins act largely through the respiratory system and that the pure food proteins investigated have little if any effect upon the disease in spite of the fact that they may give a positive skin test. If correct this observation would strongly suggest the possibility of a local tissue hypersusceptibility. In none of these cases did the ingestion of bread or other food protein giving a positive skin test cause any local symptoms in the mouth or stomach, so that, clinically at least, there was no evidence of a local sensitiveness in any other tissue.

In a recent paper on "Frequent Causes and the Treatment of Perennial Hay Fever," Walker<sup>23</sup> found the symptoms were due in 20 cases to emanation from horses, in 6 cases to cats and in a number to feathers. He speaks of similar symptoms among laboratory workers which were due to rabbit and guinea-pig hair, likewise of symptoms in bakers and housewives due to the cereal flours. Unfortunately he does not give the total number of cases studied, but since the numbers as given are small and his clinic is very large, it may be assumed that these proteins are at least infrequent as causes of perennial vasomotor rhinitis, and in so far do Walker's findings agree with my own.

<sup>23</sup> Frequent Causes and the Treatment of Perennial Hay Fever, Jour. Am. Med. Assn., 1920, 75, 782.

**Eczema, Urticaria and Angioneurotic Edema.** Forty cases of eczema were studied, 19 in children and 21 in adults. Four adults gave positive tests—3 to orris powder and 1 to egg. In no case was the finding of any clinical importance. The egg case had known of the susceptibility for many years and the eczema had persisted in spite of prolonged egg-free diet. Of the 19 children tested there were 8 cases which gave positive tests (42 per cent)—figures comparable to those of Schloss and of O'Keefe. Each one of these positively reacting children gave a positive reaction to egg-white and 4 of them gave a well-marked test to a large number of wheat proteins in addition. One child gave a test to beef, bean and pea. In no case was a single protein group involved.

The findings of these tests, with the consequent elimination of egg from the diet, brought about excellent clinical results in 4 of these 8 children, but in another patient elimination of egg had been carried out for some months before the tests were done and without any appreciable benefit to the eczema.

**Urticaria.** Out of a total of 35 cases tested, only 4 adults and 2 children gave positive results. Avoidance of the protein did not relieve the adults at all but, as in eczema, 1 of the children reacted among other things to egg, while the other reacted to wheat, buckwheat and bean, and both were improved when the corresponding foods were omitted from their diet.

Seven cases of angioneurotic edema were tested, and 2 patients gave positive tests. Both were in women who reacted to wheat as well as to one of the animal dusts, but unfortunately neither was seen again.

**Miscellaneous.** In addition to the cases noted above, in many of which protein sensitiveness is a very reasonable working basis, tests were also made in a number of other conditions not so closely related to this clinical group. These cases, 86 in number, included 19 cases of frequent colds in children, 2 of whom gave positive tests, 1 to ragweed pollen compatible with her hay fever, the other to feathers; 4 adults with chronic winter coughs were tested, 1 of whom was found positive to wheat, which finding was clinically unexplained; 6 cases with obscure chronic arthritis were tested with no positive results; 4 cases of cardiospasm were studied as completely as possible, but no positive results were obtained; 8 cases of chronic skin disease, including 3 of psoriasis, were all negative. Fifteen normal individuals were, of course, negative.

Twenty-seven patients with other conditions, including such as paroxysmal tachycardia, periodic vomiting in children, chronic headache, herpes labialis, recurrent conjunctivitis, etc., were tested with only one positive reaction in a patient, who also had late hay fever. Thus in this total group of 86 cases there were only 4 cases with positive tests, in 2 of which the tests were a mere observation without reasonable explanation.



**Summary.** In this work skin tests in 939 patients presenting various clinical conditions have been studied. It is to be expected that positive skin tests should occur together in the same protein group; that a patient with horse asthma should give a skin test to cat- or to dog-hair as well as to horse dander. Multiple tests are commonly obtained with several of the proteins in any one group, but they are also obtained to proteins in other groups. That there is no one test substance in any one group which can be used in a given case to be quite sure of ruling the entire group in or out is shown by such observations as that in the cereal group (see Chart I); many patients react to wheat proteose, but 3 adults fail to react to it, while in the animal group horse-hair and horse dander give by far the greater number of positive tests; but 2 children and 1 adult react to goose feathers and fail to react to horse at all. Thus in any given case a wide variety of tests should be done. A more perfect method of excluding proteins is to so limit the patient's diet and life that, as far as possible, contact with proteins is limited to those represented by the negative tests found.

Chart II represents a summary of the results in the various clinical conditions mentioned. It is interesting to add the tests together and then determine the relative incidence of positive results with each test substance. Chart III shows such an addition, compiled from only those cases accurately tabulated.

CHART II.—RESULTS OF SKIN TESTS IN THOSE PATIENTS TESTED WITH FIFTEEN OR MORE DIFFERENT SUBSTANCES.

Diagnosis.	Patients, total	Patients tested	Patients positive	Positive per cent
Hay fever (simple) . . . . .	347	59	25	42
Pollen asthma . . . . .	136	59	23	39.0
Horse asthma . . . . .	45	45	15	33.3
Dust asthma . . . . .	31	31	31	100.0
Food asthma . . . . .	19	19	19	100.0
Bacterial asthma . . . . .	156	103	22	21.0
Emphysema . . . . .	136	133	34	25.0
Reflex . . . . .	78	78	4	5.0
Unclassified . . . . .	47	35	3	8.5
Total asthma . . . . .	648	503	151	30.0
Vasomotor rhinitis . . . . .	198	198	45	22.7
Eczema . . . . .	40	40	12	30.0
Urticaria . . . . .	35	35	6	17.0
Angioneurotic edema . . . . .	7	7	2	28.5
Total allied conditions . . . . .	280	280	65	23.0
Miscellaneous . . . . .	86	86	4	4.6
Grand total . . . . .	1361	928	215	26.4

Figures refer to positive tests with substances other than the one to which the patient gave a history of sensitiveness.



**Discussion of the Value of Skin Tests in General.** In such conditions as hay fever, horse asthma and perhaps dust asthma, when the history shows a fairly definite and obvious relation of symptoms to some one protein, the skin test, of course, demonstrates this protein etiology. In certain doubtful cases with a suggestive history the test is of greatest value in determining whether or not the proteins suggested by that history are important or not in the etiology.

Aside from its use in diagnosis the skin test is of use in the treatment of such conditions as hay fever in order to determine the dilution of pollen extract to use at the start.

Skin tests probably demonstrate a sensitiveness to proteins in all cases in which they are positive, but it is well known that many tests are found in the clinic for which there is little if any explanation. Clinically, at least, positive tests should be taken seriously only in case they are compatible with the patient's history or in case further study and clinical experiment can prove their importance as an etiological factor.

In cases of asthma which are, at first glance, evidently dependent upon bacterial infection the skin test may often reveal a protein sensitiveness which may prove to be the fundamental starting-point of the symptoms. This is particularly true in cases of asthma which occur in the autumn and in which a test to ragweed extract is found. Such cases can best be treated by prevention the following year. In a certain relatively small number of cases, especially in children, the tests are of greatest value in demonstrating the cause of symptoms, and in most of these cases treatment by avoiding the corresponding food gives remarkable results.

In the present series there are approximately 100 cases in which positive tests of a fairly definite sort were obtained which were evidently not compatible with the history. Subsequent study showed, moreover, that in only about 13 of these cases was the *finding of the test to food or animal protein really important and of use in further treatment*. This figure is very small, but, as a matter of fact, the ability to really help a small number of patients undoubtedly justifies the great amount of routine work on many other patients. Emphasis should be placed upon the necessity of a fairly gross interpretation of any positive test. Too delicate or fine a reading merely clouds the picture and in addition renders further progress in this already obscure branch of science even more difficult.

ENZYME MOBILIZATION BY MEANS OF ROENTGENRAY  
STIMULATION.

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It is at present a recognized principle in the therapeutic application of photodynamic and radiant agents, including roentgen rays, radium, Finsen and red rays, sunlight, etc., that, apart from the direct effect on the exposed tissue, these agents may bring about a distinct systemic alteration.

Clinically this alteration is made evident in two ways: There is first of all the recognition that the effects of radiant agents may be exerted on remote pathological lesions. Thus lupus and other tuberculous processes may be benefited by light rays acting on remote body surfaces. Secondly, we recognize a general intoxication, a phenomenon of varying intensity, ranging from mere transitory and subjective symptoms to an actual fatal intoxication. To these latter forms the term roentgenray anaphylaxis has not infrequently been applied, but, of course, improperly. The general intoxication is frequently elicited when large lymphatic structures, abdominal viscera or cell-rich neoplasms or inflammatory exudates are exposed for any length of time. Walsh<sup>1</sup> is said to have been one of the first observers to record such toxic effects.

The mechanism of this reaction, apart from the assumption that it is due to the reabsorption of the products of cell destruction, has not been clearly defined. It is known that the intracellular enzymes are influenced by the agents under consideration, and experiments to study the effects upon ferments *in vitro* have demonstrated the destructive effect of radiant energy upon them, the diastasic ferment being the only one that displays considerable resistance to prolonged exposure.

Short exposures, on the other hand, may accelerate enzyme action *in vitro*, according to Richards.<sup>2</sup>

If the possibility exists that by means of irradiation the intracellular enzymes may be altered and their entrance into the blood and lymph current accelerated or retarded, it might seem a plausible method of approach to the problem of altering and controlling the amount and character of the serum ferments and the

<sup>1</sup> British Med. Jour., 1897, 2, 272.

<sup>2</sup> Am. Jour. Physiol., 1914, 35, 224

resultant effect on such local pathological processes as pneumonia<sup>3</sup> and tuberculosis.<sup>4</sup>

We cannot introduce foreign ferments directly into the circulation because of the impossibility of freeing them from more or less toxic admixtures; the advocacy of trypsin injections by Beard,<sup>5</sup> it will be recalled, was along this line but led invariably to a toxic reaction. The intestinal absorption of enzymes is likewise uncertain. The ferment-rich abdominal organs might, however, lend themselves to stimulation by means of the agents under consideration, and, as a result of varying degrees of insult, discharge ferments into the circulation in different amounts. Whipple<sup>6</sup> has noted that liver injury, for instance, causes an increase in the serolipase, and Musser and Edsall,<sup>7</sup> in studying the effect of roentgen rays on the metabolism of leukemic patients surmised that an acceleration of the proteolytic activity resulted from the roentgenray treatment. It may be permissible to quote at length from their interesting paper: "The facts that have just been mentioned demonstrated, we think, that the effect (of the roentgenrays) is not a direct one but one that requires response on the part of the individual. . . . To be more specific concerning the processes that are stimulated and accelerated by the roentgen rays, we consider that it is highly probable that the action is chiefly on autolysis. A considerable number of physiological and pathologic processes have, with considerable probability, been shown to be due to autolysis, that is, to activities that have the characteristics of ferment-like processes and that produce in their course the same classes of substances as those found in the various stages of digestion. The view is now widely accepted that the exudate in pneumonia undergoes resolution as a result of sudden autodigestion, carried out not through bacterial influences but through the activities of the tissues. . . . Following the general trend of the thought, and the direction in which the results of recent experimental work pretty generally point, the most natural explanation of the increase in tissue destruction, when this destruction is dependent upon individual body reaction, is that it is due to acceleration of autodigestive or autolytic processes. The remarkable suddenness and intensity with which the action of the roentgen rays begins immediately after exposure is more direct evidence in favor of the view that autolysis is influenced."

In a second contribution (Edsall and Pemberton<sup>8</sup>) the effect of roentgen rays on unresolved pneumonia was studied as well as

<sup>3</sup> Jobling, J. W., Petersen, W. F., and Eggstein, A. A.: *Jour. Exp. Med.*, 1915, 22, 568.

<sup>4</sup> Petersen, W. F.: *Arch. Int. Med.*, 1918, 21, 14.

<sup>5</sup> *Enzyme Treatment of Cancer*, London, 1911.

<sup>6</sup> *Bull. Johns Hopkins Hosp.*, 1913, 24, 357.

<sup>7</sup> *Tr. Assn. Am. Phys.*, 1905, 20, 291.

<sup>8</sup> *AM. JOUR. MED. SCI.*, 1907, pp. 133, 286 and 426. *Tr. Assn. Am. Phys.*, 1906, 21, 618.

attention directed to possible toxic results that might be related to the effects of the roentgen rays. In these two papers the very definite foundation for the therapeutic application of the rays in stimulation enzyme activity, thereby influencing pathologic processes, was formulated.

Since these papers of Edsall were published a considerable amount of evidence has been accumulating that tends to confirm the view that apart from the antibacterial mechanism involved in recovery from pneumonia a second mechanism, the inception of an active autolysis, plays a considerable role in the crisis (Jobling, Petersen and Eggstein,<sup>9</sup> Lord,<sup>10</sup> Weiss,<sup>11</sup> Blake and Cecil,<sup>12</sup> Petersen and Short,<sup>13</sup> Thomas and Parker,<sup>14</sup> etc.).

In the meantime there has developed, first quite empirically, the so-called non-specific method of treatment of a number of diseases whereby disease processes are either abruptly terminated or markedly influenced by the intravenous injection of a great number of different agents ranging from chemicals—salts, formalin, etc.—through the metallic colloids—silver, arsenic, etc.—to various biological substances—vaccines, milk, protein split products, etc. The intensive study which interest in this field has stimulated, has led to the recognition that the broad basis of this form of therapy rests on common systemic alterations produced by these various substances. Weichardt<sup>15</sup> uses the general term "plasma-activation" to cover the whole series of alterations inaugurated by the non-specific injections. Among these the alteration in the permeability of the cells is perhaps fundamental. The serum enzymes, too, have been found altered, particularly the proteolytic enzymes are seemingly increased in amount. Lindig,<sup>16</sup> Luithlen<sup>17</sup> and others regard this mobilization as of particular significance. Sachs,<sup>18</sup> in his recent review, seems to be of the same opinion.

Considering the fact that the enzyme mechanism very probably plays a role in such pathological conditions as pneumonia and tuberculous infection, and that even in the non-specific reaction the effect of enzyme mobilization is supposed to be of some importance, we thought it might be of interest to study whether by means of the roentgen ray or other similar agents we could bring about the "shedding" of organ enzymes. Studies heretofore reported, such as those of Hall and Whipple,<sup>19</sup> are concerned chiefly with the cause of the roentgen ray shock when large doses are used, while Denis, Martin and Aldrich<sup>20</sup> endeavored to elucidate the same point

<sup>9</sup> Exp. Med., 1915, 22, 568.

<sup>10</sup> Jour. Am. Med. Assn., 1919, 73, 1420.

<sup>11</sup> Arch. Int. Med., 1919, 23, 395.

<sup>12</sup> Jour. Exp. Med., 1920, 31, 445.

<sup>13</sup> Jour. Infect. Dis., 1918, 22, 147.

<sup>14</sup> Arch. Int. Med., 1920, 26, 125.

<sup>15</sup> München. med. Wehnschr., 1918, 65, 581.

<sup>16</sup> Ibid., 1919, 66, No. 33.

<sup>17</sup> Wien. klin. Wehnschr., 1913, 26, 653.

<sup>18</sup> Therap. Halbmonatschr., 1920, 34, 379.

<sup>19</sup> AM. JOUR. MED. SCI., 1919, 157, 453.

<sup>20</sup> Ibid., 1920, 160, 555.

by means of massive regional doses in rabbits. Pfeiffer,<sup>21</sup> on the other hand, has already demonstrated that in photodynamic intoxication (he used "rose bengale") a mobilization of serum peptidase takes place.

Apart from the mobilization of enzymes the selective stimulation of organs by means of the roentgen ray or related agents is a related field in which therapeutic applications have been reported only in very recent papers. These include the alteration in the coagulation mechanism following raying of the spleen (Stephan<sup>22</sup>) and the effort to increase the function of certain of the glands of internal secretion by means of stimulating doses.

**Experimental.** Preliminary experiments were carried out to determine whether variation in enzyme titers occurred in the serum following roentgen ray exposure of the liver, intestinal and splenic area.

*Liver Exposure.* Dog of 14 kilo. Diet, June 13 to 29, 1917, as follows:

Protein (lean meat)	220 gm.
Carbohydrate (cracker meal)	60 "
Fat (lard)	40 "
Bone ash	35 "
Water	300 "

From June 29 to the termination of the experiment the daily ration was altered so that the animal received 100 gm. of carbohydrate and 25 gm. of fat per day. The normal metabolism of this diet was first studied for a period of several days.

On June 20 (10 A.M.) the liver area was rayed for fifteen minutes (Coolidge tube, 10-inch distance, 8 ma. and 5-inch back spark; no screen). On June 25 the liver was exposed for thirty minutes (8-inch spark) and on June 29 for one hour. (In raying the liver area, parts of the gastro-intestinal tract, pancreas, etc., were, of course, not to be excluded). After a period of four days a superficial burn followed over the area exposed. The animal was killed on July 5. No gross or microscopic alterations were to be found in the abdominal viscera.

It was observed that:

(a) The weight of the animal decreased after the second exposure. (about 1000 gm.)

(b) That the nitrogen excretion also increased after this exposure. The serum studies revealed the following changes:

(c) Exposure was followed by a transient decrease in the non-coagulable nitrogen of the serum with an increase in the amount later. From the original of about 40 mg. per 100 cc the non-coagulable nitrogen increased to 55 mg. at the end of the experiment.

<sup>21</sup> Ztschr. f. Immunitätsforsch., orig., 1915, 23, 597.

<sup>22</sup> München. med. Wchnschr., 1920, 67, 309.

(d) A marked mobilization of the protease followed the short exposure and there was no change following the two longer periods of exposure to the rays.

(e) The ereptase (peptidase) was increased after the short exposure but immediately decreased after the longer periods.

(f) The lipase (esterase) titer increased after the first two exposures but decreased after the longer period.

(g) The anti ferment titer was quite irregular but gave evidence of a distinct increase after the final exposure.

(h) The diastatic activity fluctuated to a considerable extent, but, was as a rule, augmented after the roentgenray exposure.

It was apparent from the experiment that as a result of the roentgen-ray exposure the serum ferments were not only altered quantitatively, but that decided differences in reaction were obtained with different degrees of exposure and consequent stimulation of the liver parenchyma.

*Intestinal Exposure.* In the following experiment a dog of 19½ kilos was used. The diet was as follows:

Protein . . . . .	330 gm.
Carbohydrate . . . . .	130 "
Fat . . . . .	35 "
Bone ash . . . . .	40 "
Water . . . . .	400 "

Because of the rejection of about 375 gm. of the diet on the two-day period following the second exposure the diet was reduced on July 24 to:

Protein . . . . .	200 gm.
Carbohydrates . . . . .	100 "
Fat . . . . .	20 "
Saline . . . . .	20 "

The water ration was increased to 600, later to 2000 cc per day.

The animal was rayed for periods of time similar to the first, but in this case the upper abdominal viscera were protected so that only the lower intestinal area was exposed. (Distance, 10 inches; 8 ma.; 6-inch spark; no screen).

(a) The weight of the animal decreased after the second exposure. This decrease, not associated with a corresponding increase of nitrogen excretion, was probably due to a loss of water content of the animal. The serum alterations revealed the following:

(b) A distinct transient increase in the non-coagulable nitrogen after the periods of exposure. There was no permanent alteration of the original amount (25 mg. per 100 cc).

(c) Only a slight and transient increase in the protease following the original exposure; no increase after the longer periods of raying.

(d) A considerable augmentation of peptidase, reaching the maximum after the second exposure; a decrease after the longest exposure.



(e) A lipase curve similar to that following the liver exposure.

(f) Marked fluctuations in the antiferment titer, with less evidence of reaction following the final exposure than in the case of the liver.

(g) A sharp increase in the diastase after the first two exposures; no change following the longest period.

On the basis of these preliminary experiments we have made a more detailed study of the serum changes following roentgenray exposure of the liver and intestinal and splenic areas in dogs. They were rayed for the following periods: five minutes, ten minutes and twenty minutes with Coolidge tube screened by a 3-mm. aluminum screen, 10-inch distance; 8 ma.; 5-inch backspark and a final unscreened exposure of twenty minutes. The time interval between the exposures varied from five to fourteen days. The exposures were made in the morning, serum samples being obtained before, one-half, five, twenty-four, forty-eight and seventy-two hours after the exposure. The samples were always taken before the animals had been fed.

The following observations were made:

Temperature.

Leukocyte count—differential.

Coagulation time—capillary tube method.

Urine: Volume. Total nitrogen excretion.

Serum enzymes: Protease.

Ereptase (peptidase).

Lipase.

Diastase.

Complement titer.

Antitrypsin titer.

*Temperature Changes.* The temperature of dogs is, of course, irregular, but we have made observations of the rectal temperature of animals in whom the liver, spleen and intestinal region were rayed.

With moderate dosage (five and ten minutes) little effect was observed, as will be apparent in the following records:

	Before raying.	30 minutes after.	1 hour after.	5 hours after.	24 hours after.
LIVER:					
Dog No. 10	102.0° F.	103.8° F.	102.4° F.	103.0° F.	104.6° F.
Dog No. 13	102.4° F.	102.4° F.	102.4° F.	102.8° F.	101.4° F.
SPLEEN:					
Dog No. 12	103.0° F.	103.4° F.	102.4° F.	102.6° F.	101.8° F.
INTESTINE:					
Dog No. 11	101.4° F.	102.8° F.	102.0° F.	101.8° F.	101.8° F.

When the longer dosage (twenty minutes, with or without screen) was given the temperature changes were of greater amplitude and consistency.

SPLEEN:					
Dog No. 8	101.4° F.	102.2° F.	103.6° F.	104.2° F.	102.0° F.

There was no apparent difference in the degree of reaction whether the splenic, intestinal or liver region was rayed.

*The Leukocyte Count.* The leukocytic reaction showed considerable differences with the different regions stimulated. In the following tabulation the normal count taken before the roentgen-ray exposure is contrasted with the average of the counts obtained for the half-hour, one-hour, five-hour, twenty-four-hour, forty-eight-hour and seventy-two-hour periods:

	Liver.	Spleen.	Intestine.
Normal . . . . .	4,000	10,000	3,000
After five hours exposure . . . . .	7,600	16,700	3,400
Before . . . . .	3,200	14,200	3,000
After ten minutes exposure . . . . .	5,600	13,400	8,200
Before . . . . .	3,400	11,400	7,400
After twenty minutes exposure . . . . .	10,000	11,300	12,900
Before . . . . .	4,800	13,700	14,300
After twenty minutes exposure, (without filter) . . . . .	8,100	14,300	17,450

In the first chart (I) the average leukocyte count (each curve representing the average of two dogs) following raying of the liver (*A*) splenic, (*B*) and intestinal, (*C*) areas for the various periods is shown. In these experiments the spleen dogs had a relatively high leukocyte count before the experiment was commenced. It will be observed that considerable differences in the type of response become manifest. The short sharp rise of the liver exposure is in contrast to the step-like effect of the intestinal exposure. Incidentally the latter reaches the maximum of reaction following the final exposure without filter. Raying of the splenic area evidently does not stimulate leukocytosis to any comparable degree. This corresponds in general with the observations previously recorded in the human and in experimental animals other than dogs.

*The Differential Count.* The differential count of the leukocytic response following the roentgen ray showed some variation, the chief difference being observed in a rather marked eosinophilia following the raying of the liver region. This effect is shown in the following table:

	Polymorpho- nuclear leukocytes. Per cent.	Small Mononuclears. Per cent.	Large mononuclears. Per cent.	Eosin. Per cent.
Normal . . . . .	67	27	4	2.0
One-half hour after five min- utes exposure of liver region	65	26	4	5.5
Five hours . . . . .	77	15	3	4.5
Twenty-four hours . . . . .	63	20	0	17.0
Forty-eight hours . . . . .	62	21	6	11.0
Seventy-two hours . . . . .	62	24	7	7.0

The eosinophilia reached its maximum after raying for 10-minute periods (average 11 per cent eosinophiles), but with the longer exposures was no longer so marked. It was observed in three of four dogs studied.



Raying of the intestinal area and of the splenic area was followed by a fairly constant diminution of the mononuclear elements and a relative increase in the polymorphonuclear leukocytes. Nucleated red cells were occasionally observed in this group of animals; myelocytes seemed to occur more frequently in the blood after raying the liver, although a considerable number were observed after the more intense raying of the spleen.

*Blood Coagulation.* In studying the coagulation time we made use of capillary tubes drawn out to uniform caliber and the clotting time recorded when on breaking the tube a firm coagulum could be drawn out. A number of recent investigators, observing the reduction of the coagulation time following the raying of the splenic area have suggested that measure for therapeutic use in cases of hemorrhage. It is known that the raying of tumors and of lymphatic structures results in this effect on the coagulation. In our experiments the most prompt effect on the clotting time seemed to follow raying of the lower intestinal tract; the effect on the clotting time following raying of the splenic area was more delayed. In the latter case, however, the effect on the coagulation, especially after the longer raying periods, was more prolonged in effect.

In the following chart the average coagulation time is shown for the various periods:

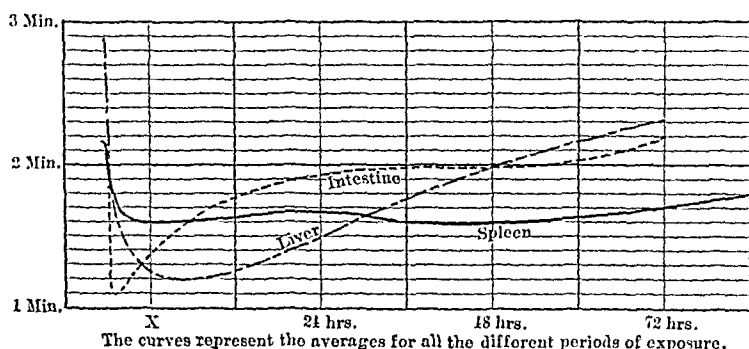


CHART II.—Coagulation time of blood after raying liver, intestinal and splenic areas.

*Nitrogen Excretion.* Kjehldahl determinations were made in duplicate of the urine nitrogen excretion. Using the relatively moderate doses of roentgen rays indicated we were not able to determine an increase in the excretion of nitrogen as a result of the exposure except in the case of the liver area, where raying for the longest time periods (twenty minutes) resulted in an increase of the average excretion:

Average for three days before raying . . . . .	1.3 gm.
Average for four days after exposure (including day of raying) . . . . .	2.1 "
Average for the next four days . . . . .	1.7 "

Raying of the intestinal and splenic area had no such effect.

The non-coagulable nitrogen of the serum was never greatly altered, the only marked changes appearing in the serum after liver raying. The average NC nitrogen of the serum after ten minutes' raying was as follows (four animals):

	Normal, mg.	30 minutes after, mg.	1 hour after, mg.	5 hours after, mg.	24 hours, mg.
Liver area (per 100 cc) . . .	21	23	31	30	29
After raying the intestinal area (three animals) (per 100 cc) . . . . .	30	30	29	30	32
Splenic area (three animals) (per 100 cc) . . . . .	17	18	17	17	17

With the longer periods of raying (twenty minutes with and without filter) the effects were even less apparent. Judging from Hall and Whipple's<sup>23</sup> results we may assume that we were dealing with relatively non-toxic doses, since in their animals which were given large and lethal doses the non-protein nitrogen of the serum was increased to a considerable degree.

**Enzymes.** *Protease.* Protease in the serum was determined by the chloroform method and the values represent the amount of nitrogen digest per cc in milligrams (twenty-four hours at 37° C.). It is apparent from a survey of the curves plotted in Chart III that differences in the extent of enzyme mobilization depended on the amount of roentgenray exposure as well as the area rayed.

The liver (III A) and intestine (III B) dogs had practically no protease present in the serum before raying and were not influenced by the smallest dose (five minutes). With exposure extended to ten minutes the intestine dogs responded by a prompt mobilization, the effect on the liver dogs being apparent as a somewhat delayed reaction, but persisting to the time of the next exposure. In this case exposure for twenty minutes again increased the amount of protease. A maximum effect for the liver exposure in these two dogs evidently lay between the ten and twenty-minute periods.

The spleen dogs (III C) differed to the extent that the initial serum titer tested before exposure contained a considerable amount of protease. (These two animals had an average leukocyte count of 10,000 as contrasted to the average of 3000 and 4000 for the intestine and liver animals.) Even the short roentgenray exposure resulted in a diminution of the titer, which, however, was recovered and even augmented before the second period of exposure. This second exposure (ten minutes) was followed by a slight increase and then a progressive diminution.

<sup>23</sup> AM. JOUR. MED. SCI., 1919, 157, 453.

*Peptidase* (Erepsin). The presence of a peptone-splitting enzyme in the serum has been reported at various times for several of the smaller laboratory animals as well as in the human. Our inability to secure glycyltryptophan compelled us to resort to Witte peptone, as reported in a previous paper (Petersen and Short<sup>24</sup>). The titer which we have used represents the minimum dilution of serum which in twenty-four hours' digestion still gives a definite tryptophan reaction with bromine water.

From a study of the curves (IV *a, b, c*) two distinct changes are apparent: First, that there is no correlation between the amount of proteolytic and peptolytic enzyme action in the serum. While in one increase a considerable amount of proteolysis may occur, there is no increase in the erepsin, or *vice versa*. On the other hand in periods when the one enzyme is increasing in titer the other enzyme may be diminishing its titer. (Charts III A and IV A.) Secondly, there is a decided difference in the response of ereptase with the raying of the different regions. The greatest and most persistent increase takes place following the raying of the gastro-intestinal tract. Raying of the splenic area seemed followed by least effect on the peptidase content.

*Lipase*. Serum lipase was titrated by the ethylbutyrate method and the charts represent the amount of free fatty acid liberated from 1 cc of ethyl butyrate by 1 cc of serum in twenty-four hours' incubation, and is expressed in terms of  $\frac{N}{500}$  HCl. (Chart V, *A, B, C*)

*Diastase* (Amylase). Diastase in the serum was tested by the Wohlgemuth method, modifying the amount of the starch substrate (1 cc of 0.5 per cent solution of soluble potato starch), incubation being for twenty-four hours. It was found that the fluctuations of the diastase titer were very great, depending very probably on whether or not portions of the pancreas were included in the field of raying. The rôle of the pancreas, as well as other possible sources of blood amylase, has been discussed by King.<sup>25</sup> As a rule, raying of the liver area was followed by a greater mobilization of diastase than in the lower intestinal or splenic areas. In Chart VI the serum diastase expressed in Wohlgemuth units following a ten-minute exposure over the liver is illustrated.

*Antiferment*. Antiferment fluctuations following roentgen-ray stimulation were of considerable range, some of the exposures being followed by an increase and other by a decrease in the titer. In the table on page 118 (which shows the inhibition in percentage for the single serum unit, usually 0.025 cc serum, the antiferment alterations following raying of the splenic area are shown, together with the average.

<sup>24</sup> Jour. Inf. Dis., 1918, 22, 147.

<sup>25</sup> Am. Jour. Physiol., 1914, 35, 301.

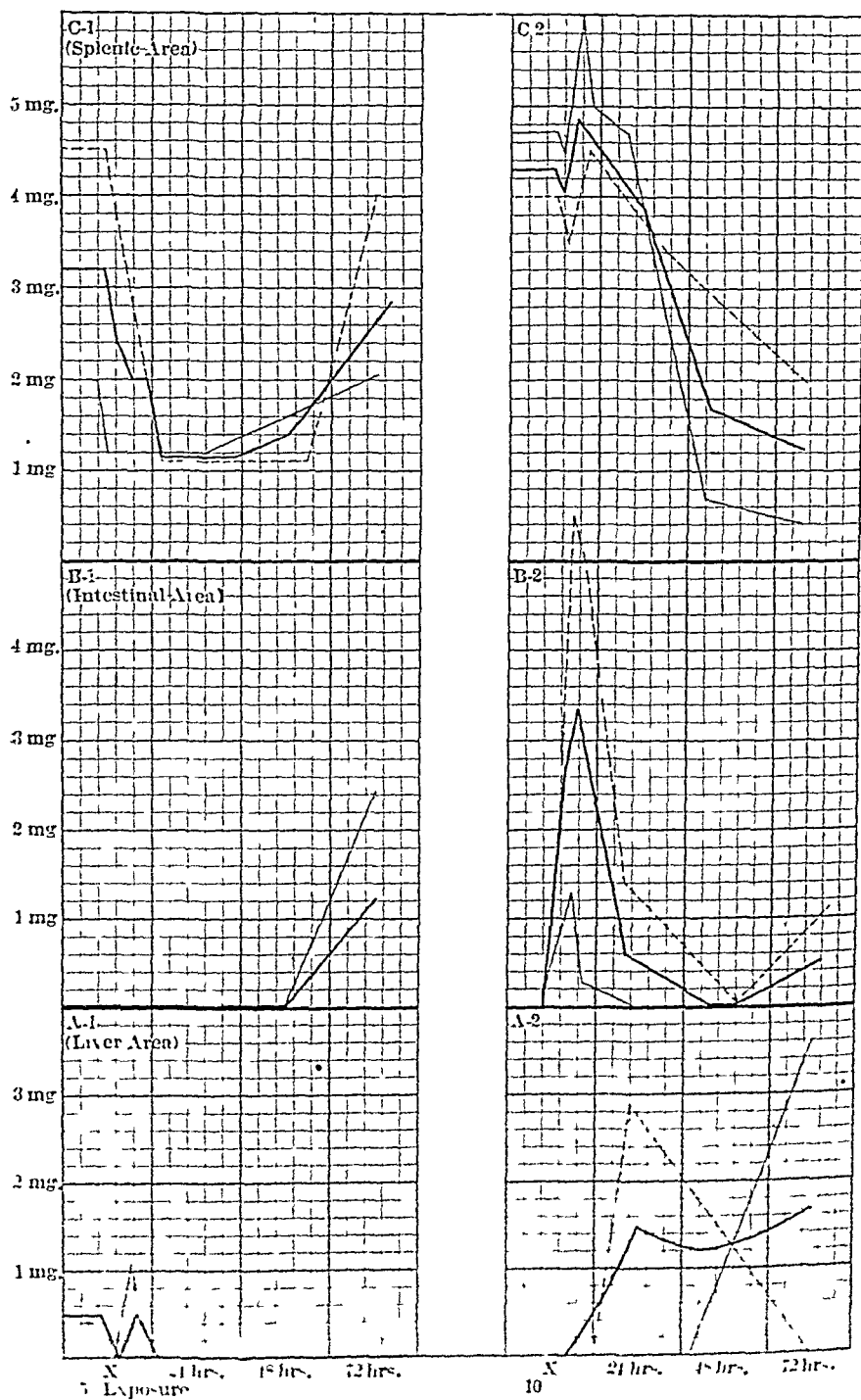
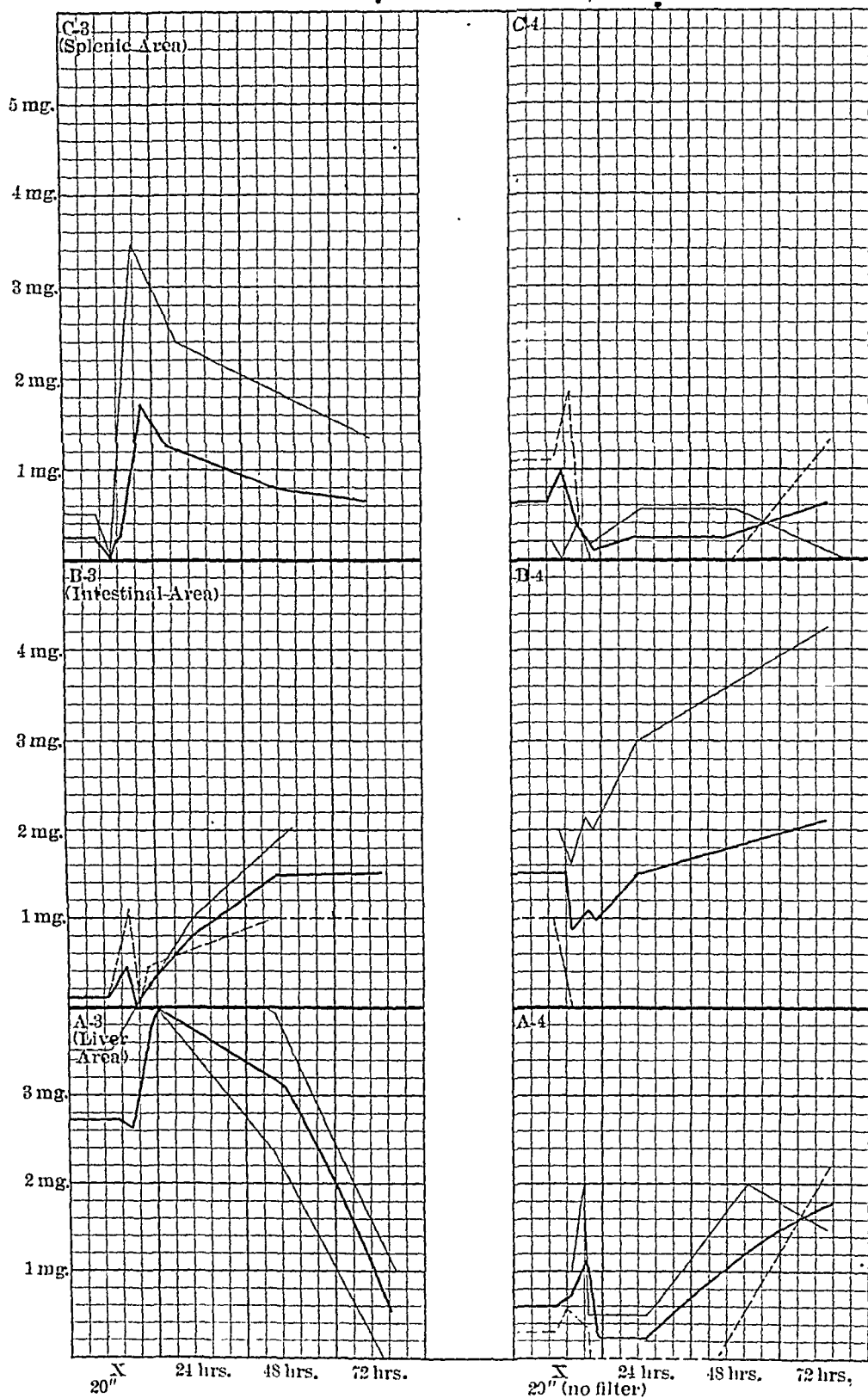


FIGURE III — Mobilization of serum protease



following irradiation of various organs.



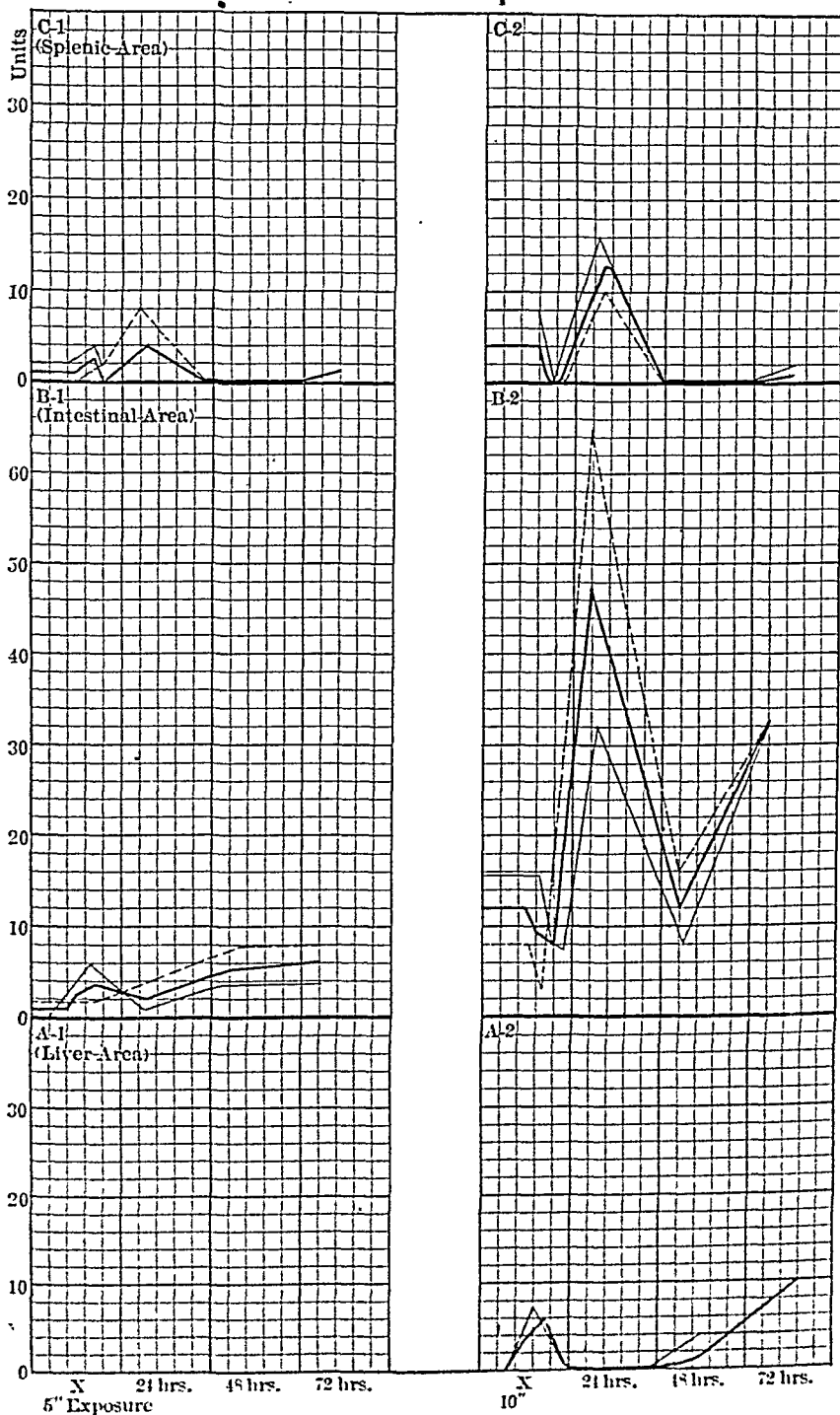
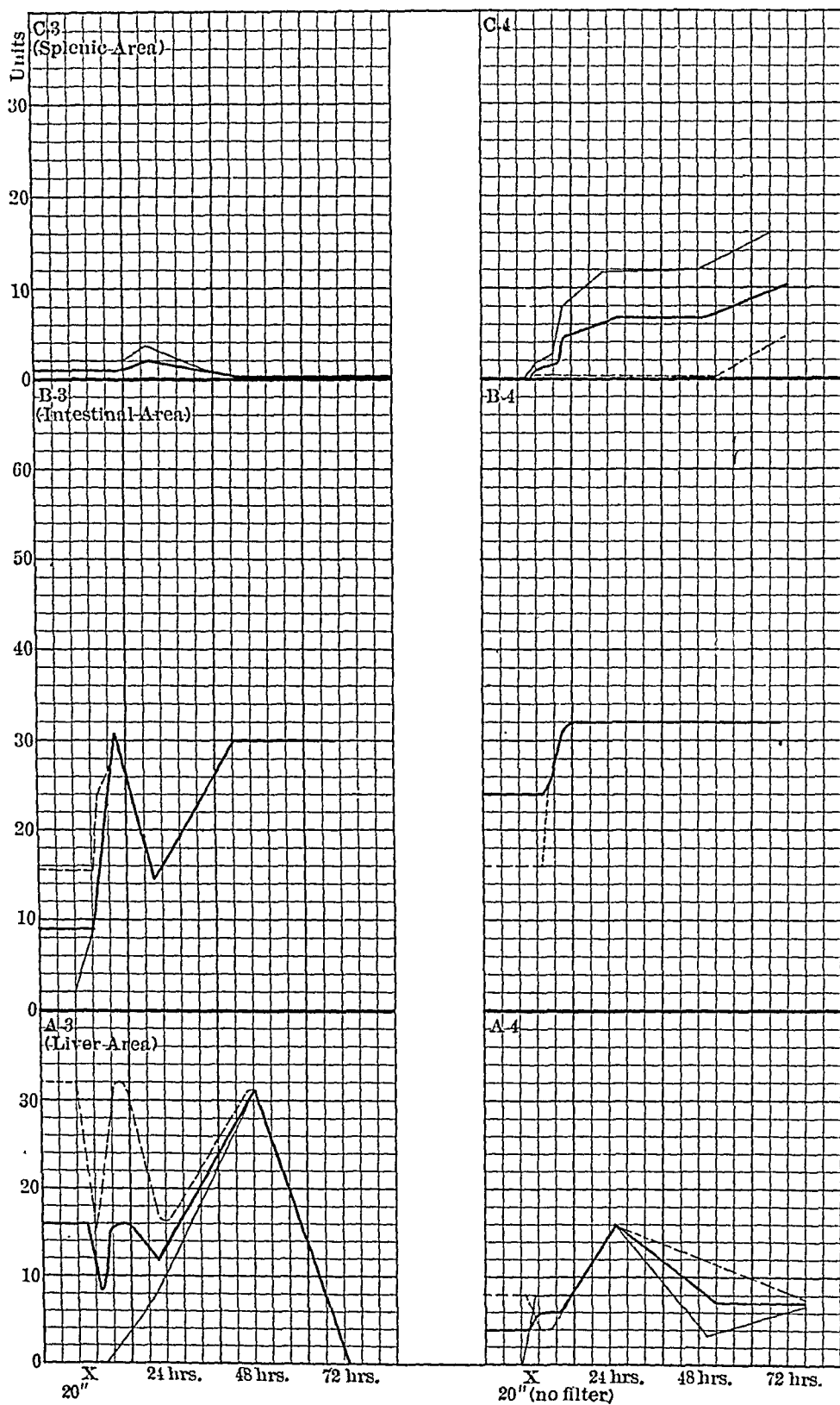


CHART IV.—Mobilization of serum



peptidase after regional irradiation.

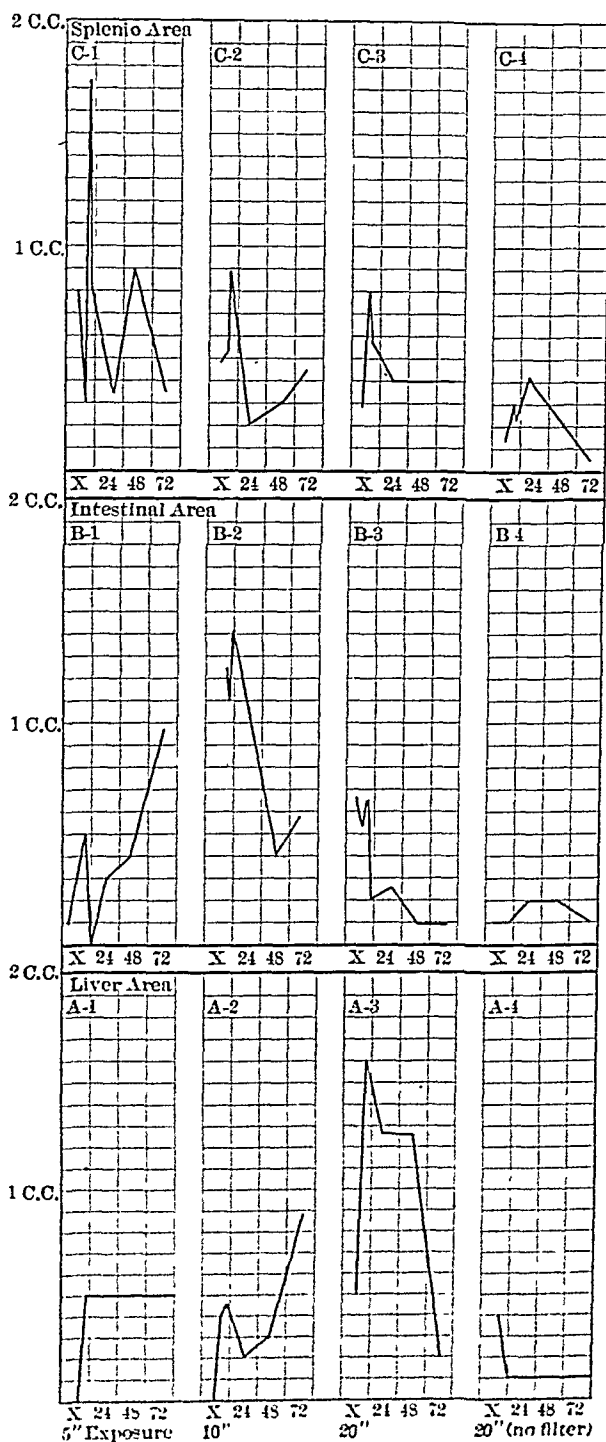


CHART V.—Lipase titer following regional roentgenray stimulation.

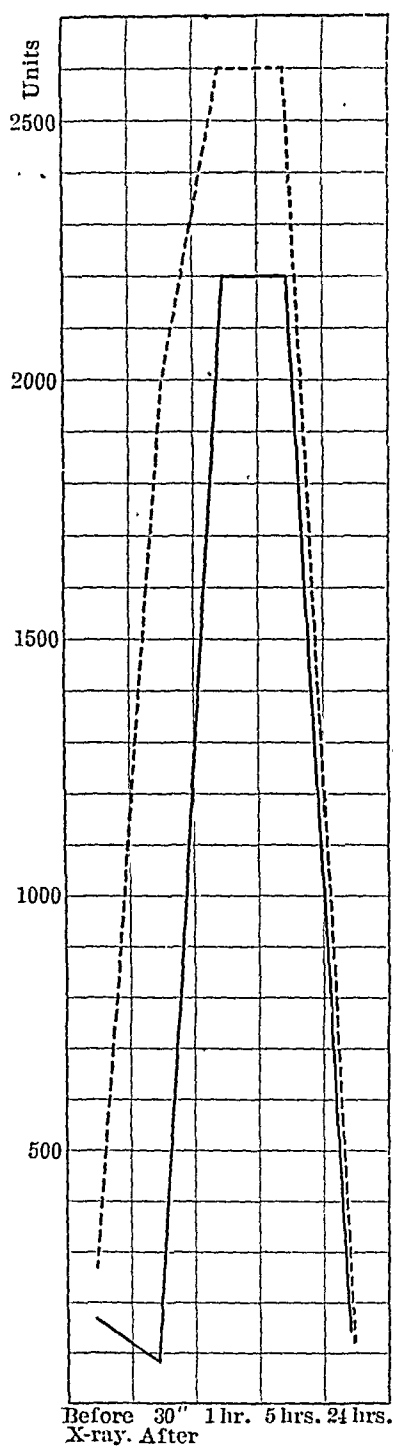


CHART VI.—Diastase titer following liver X-ray (ten-minute exposure).

Before, per cent.	Minutes' exposure.	After 30 minutes, per cent.	1 hour, per cent.	5 hours, per cent.	24 hours, per cent.	48 hours, per cent.	72 hours, per cent.
0	10	50	0	50	20		
65	5	65	65	30	65	65	55
50	10	70	65	58	77	66	75
75	20	75	75	75	65	70	78
65	20	70	72	75	72	70	70
75	5	50	58	35	58	58	60
57	10	60	33	25	15	25	35
40	20	68	72	58	78	80	66
34	20	50	50	60	40	44	40
Average							
51		62	54	51	54	60	60

**Discussion.** The data presented in this paper seem to us to have a direct bearing on certain therapeutic applications of the roentgen ray and other related photodynamic and radiant agents, applications which heretofore seem to have been ignored because of the more obvious and direct uses of such agents in diagnosis or in local therapeutics. It is only in the relatively recent recognition of the value of heliotherapy in tuberculosis that we find evidence of this use of the indirect and systemic effect of a photodynamic agent.

Here the experience has been that such stimulation (heliotherapy) has a dual clinical effect in tuberculosis.<sup>25</sup> In the active case it is in general harmful because of an increased tendency to hemorrhage, augmentation of the temperature range, the amount of secretion, etc., all bearing evidence of an increase of focal activity of digestion of the connective tissue bulwark. In the quiescent case the clinical experience is, on the whole, favorable, the general resistance of the patient being apparently increased, the weight, the blood picture and subjective symptoms of the patient improved. This dualism in clinical effect we meet with in practically every agent used in the treatment of tuberculosis. We find it true of tuberculin. We find it true of the more recent non-specific methods: albumoses (Holler<sup>27</sup>), milk (Schmidt<sup>28</sup>), casein (Lindig<sup>29</sup>).

We are not yet familiar with the fundamental changes that underly heliotherapy or non-specific therapy, or specific tuberculin therapy for that matter. Very probable are the conclusions of Luithlen<sup>30</sup> and Starkenstein<sup>31</sup> and others that we have to deal primarily with changes in the permeability of the cells. According to this conception practically all the other recorded observations—changes in blood-forming organs, in clotting time, the fever and defervescence, the effect on the nervous system, on joints, liver and eye tissues, the increase in resorption of exudates, increase in mus-

<sup>25</sup> Pottinger, F. M.: *Interstate Med. Jour.*, 1915, 22, 818.

<sup>27</sup> *Beit. z. klin. der Infektionskr.*, 1917, 6, 92.

<sup>28</sup> *Deutsch. Arch. f. klin. Med.*, 1919, 131, 1, and with Krauss, *Deutsch. med. klin.*, 1919, 15, 503.

<sup>29</sup> *Arch. f. Gynäk.*, 110, No. 3.

<sup>30</sup> *Loc. cit.*

<sup>31</sup> *München. med. Wehnschr.*, 1919, 66, 205.

cular work and gland secretion, the increased resistance to intoxication—are merely the expressions in the various cell groups of such cell-membrane alterations. So, too, the enzyme mobilization which has been repeatedly suggested as the cause of the clinical improvement might be regarded as the result of the alteration in permeability.

With this in mind it seemed of some value to ascertain whether or not enzymes could be mobilized as a result of raying the abdominal organs, and if so, could qualitative differences be maintained by raying various organ complexes. The experiments here reported seem to bear out this assumption. Depending on the intensity of the roentgenray stimulation one can determine a maximum effect (which in our cases varied from ten to fifteen minutes' exposure), diminishing in either direction from a dose that was too small to cause appreciable differences (five minutes) to doses that were too large (twenty minutes to one hour). With these latter doses there was an actual diminution in the amount of serum enzymes titrated. Such a result is one that we might anticipate. Moderate doses will conceivably stimulate both cell activity in general and enzyme action itself, according to Richards's<sup>32</sup> experiments; larger doses would either leave that activity unaltered or result in an actual destruction of the enzymes.

In these experiments it is to be kept in mind that it is impossible to confine the roentgenray stimulation to any single organ. In raying the liver both the intestine and the pancreas would necessarily be included to some extent, as they would be, too, in raying the splenic area. In raying the intestinal area we endeavored to ray the lowest quadrant to avoid the simultaneous stimulation of other organs. It is also to be kept in mind that because of the duration of the periods of raying the blood and its elements must have passed through the rayed area many times. Some of the enzyme effect might have been derived from the leukocytes, which in the dog are relatively rich in proteolytic enzymes.

As previously stated, little attention has so far been paid to the possibility of organ stimulation by means of the roentgenray. Manoukhine<sup>33</sup> alone has carried out a series of experiments in tuberculosis. He rayed the spleen of tuberculous guinea-pigs and monkeys for varying periods and noted that such animals outlived his control animals for a considerable time, while animals in which the liver was rayed were unfavorably influenced. Manoukhine decided that when the spleen was rayed leukocytolysins were liberated, which, while destroying leukocytes, aided the organism in combating infection. When, on the other hand, the liver was rayed, leukocyte-protecting substances were formed and thrown into the circulation. Manoukhine treated a few human cases with encouraging results. Whatever the interpretation of the mechanism, these experiments

<sup>32</sup> Loc. cit.

<sup>33</sup> *Wratsch Gazeta*, 1914, 15, 617.

bring the evidence that by means of selective organ stimulation therapeutic effects may be achieved.

The spleen and its relation to resistance to tuberculosis has in recent years been studied extensively, more particularly in connection with mononuclear-cell reactions and the effect of extirpation and roentgenray exposure thereto. It might seem possible that along with the cellular reaction the serum alterations suggested in this paper resulting from roentgenray stimulation of selected organs may have a part in the phenomena of altered resistance to tuberculosis.

**Conclusions.** By means of selective organ stimulation by roentgen rays in moderate dosage it seems possible to influence the serum enzymes to a considerable degree. Such doses act in stimulating a mobilization of various enzymes; large doses lessen the titer of the serum enzymes.

Raying the hepatic area in dogs resulted in a temporary leukocytosis (with eosinophilia) as well as a well-defined increase in the titer of protease, peptidase, lipase and diastase in the serum.

Raying the intestinal area resulted in a more persistent leukocytosis and a marked mobilization of peptidase; the other enzymes were altered less in proportion.

Raying of the splenic area was followed in general by a diminution of the serum enzymes with the exception of the lipase.

Alteration in the coagulation time of the blood following raying was not confined to raying of the splenic area but followed exposure of the other regions as well. No alterations of complement titer were observed following organ stimulation. The antiferment was usually increased after periods of raying.

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## THE RELATION OF THE PITUITARY GLAND TO EPILEPSY.

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SINCE the publication of Cushing's memorable monograph on the hypophysis,<sup>1</sup> increasing interest has been directed to the possibility of an endocrine factor or factors as the causative agent of those convulsions which are classed under the broad term "epilepsy." With further knowledge of the functions of these glands the body of evidence as reflected in the literature has rested on the pituitary element as the predominating factor in the so-called "endocrine epilepsies," although some writers following the lead of Laignel-Lavastine<sup>2</sup> believe the thyroid is the glandular element at fault.

<sup>1</sup> The Pituitary, 1911, W. B. Saunders Company, Philadelphia.

<sup>2</sup> The Internal Secretions and the Nervous System, 1919, Nervous and Mental Disease Publication Company.

For the past year every case of epilepsy coming to the Washington University Dispensary, St. Louis, and remaining under careful observation for a minimal period of three months has been studied from the point of view of a possible endocrine dyscrasia, more particularly one referable to the hypophysis. Our series consisted of 16 cases, representing all types and degrees of presumed epileptic convulsions without regard to any pre-supposed etiological factors except tumors. The average duration of the illness was five and six-tenths years, the extremes being six months and fourteen years.

Each case was investigated according to the following routine procedure:

1. Careful history.
2. Complete general including neurological examinations.
3. Mental tests using the Yerkes-Bridges point scale, in some cases correlated with the Binet-Simon tests.
4. Wassermann reaction on the blood and in several cases the spinal fluid.
5. Ophthalmoscopic examination of the fundus; tests of vision by the usual methods.
6. Visual fields by perimetry.
7. Lateral stereoscopic roentgen-ray plates of the skull.
8. Other examinations when indicated, such as cystoscopy, rhinoscopy, etc.

Before instituting treatment, some experiments to determine the relative potency of various commercial pituitary products were performed in the pharmacological laboratory through the courtesy of Dr. E. K. Marshall, Jr. Using as an index the amount of contraction of the isolated uterus of a virgin guinea-pig, according to the method of Roth,<sup>3</sup> we found a wide variation in the efficacy of the preparations on the market, and even of different lots of the same manufacturer. The least variable were found to be the posterior lobe extract of Parke, Davis & Co. (pituintrin) and the whole gland extract of Burroughs, Wellcome & Co (pituitary extract-whole gland), and these were adopted for this study.

All previous medication was discontinued and the patients were given varying doses hypodermically of one of the above-mentioned products or in a few instances the desiccated whole gland (Burroughs, Wellcome & Co.) by mouth. The average initial dose was 0.5 cc, increasing subsequently according to the tolerance of the patient. The number of ensuing attacks, the amount of pituitary substance administered, and the body weight were carefully charted and will be referred to later.

Before discussing our results a brief summary of each case, detailing only positive findings, may be of value.

<sup>3</sup> U. S. P. H. S. Hygien. Lab. Bull., 1916, No. 109.



CASE I (W. U. D., A29991).—Miss C. M., aged twenty-two years, whose family and past history were negative, has had convulsions since she was nine years old, during which time she had clonic spasms, more often on the right side. No auræ, hallucinations or delusions. Since her eighteenth year she has often had six attacks daily.

*Physical Examination.* Hypertrichosis of the upper lip and chin. Pupils equal, right slightly notched. Slight corneal anesthesia. Tongue on protrusion favors the right side. Cardiac examination showed occasional extrasystoles. Pulse-rate, 82. Blood-pressure, 115-80. Abdomen negative. Reflexes entirely normal. Mental examination showed what Dr. G. B. Smith termed a "typical epileptic constitution," with some scattering of the tests and retardation. Blood Wassermann negative (both antigens). Fundi normal. Lateral stereoscopic plates of skull (Dr. S. Moore) disclosed a small, long, shallow sella turcica. Clinoid processes drawn out into a point. The posterior portion of the skull increased in thickness and has general lack of detail in skull structures.

The patient was given an average of 1 cc of the posterior lobe extract weekly for two months, but the attacks became more frequent. Nine months later she reports feeling better since the treatment was discontinued.

CASE II (W. U. D., 38541). Master L. W., aged fifteen years, came of a normal family. Blindness had been discovered when thirteen months old. Attacks began a year ago, and there have been five subsequent convulsions, although for the past three months his mother states that the patient has had daily "spells of unconsciousness," but does not fall.

*Physical Examination.* Head small, high, narrow. No prognathism. Pupils small and equal. React to light but not to accommodation. Ophthalmoscopy showed a bilateral optic atrophy. Patient has faint light perception. Head otherwise negative. Chest and abdomen negative. Sparse axillary and pubic hair. Normal external genitalia. Blood-pressure, 92-60. Reflexes entirely negative. No Trousseau or Chvostek. No increased excitability to galvanic current. Astereognosis more marked at finger tips than in palm. No sensory changes. Mental tests were applied with difficulty, for there are few tests that fit a patient of this description, especially since he was unable to use his finger tips. There was evidently some mental deterioration not accounted for by his blindness. Deterioration probably progressive. Urine negative. Blood Wassermann negative. No record of roentgenograms of the skull. Posterior lobe given for four months. Whole gland subsequently administered for two months. During this period patient had eight severe and seventeen light attacks, so the treatment was discontinued.

CASE III (W. U. D., A8224).—Miss I. K., aged thirty-one years, whose family and past history were negative, has had epilepsy since she was twenty. Convulsions recently have occurred once or twice weekly.

*Physical Examination.* Facial acne (bromides?). Hypasthenic, rather emaciated. Examination quite negative. Blood-pressure, 96-75. Mental examination showed mental adult age of superior mentality as regards judgment and ability to work. Vision, both eyes, 20-24. Ophthalmoscopic examination: Disk edges blurred and irregular; retinæ pale but vessels normal; deep physiological cupping; visual fields normal. Urine negative. Phenolsulphone-phthalein kidney functional test: First hour, 33 per cent; second hour, 13 per cent. Blood Wassermann negative.

Stereoscopic lateral plates of the skull showed practically an approximation of the anterior and the posterior clinoid processes, but no apparent bony bridging. Sella possibly a trifle deepened. Posterior lobe extract given for four months with no amelioration of symptoms.

CASE IV (W. U. D., A17278).—Mrs. M. J., aged fifty-two years, negress, had a normal family and past history. Onset of attacks four years ago, with subsequent monthly seizures unaccompanied by auræ.

*Physical Examination.* Pupils slightly irregular. Reactions normal. Teeth in poor condition (subsequently extracted). A small thyroid is palpable. Romberg, slight swaying. Examination otherwise negative. Blood-pressure, 120-84. Mental tests if anything above the average. If there is any retardation due to epilepsy it is quite slight. Vision: O. D., 20-15; O. S., 20-19. Ophthalmoscopic examination: Beginning cataract lower nasal quadrant of either lens. No abnormalities of the fundus. Visual fields normal. Urine negative. Wassermann on blood negative. Lateral stereoscopic plates of skull: Skull very long; edentulous mouth; sella normal. Posterior lobe extract administered for five months but attacks were not altered in severity or frequency.

CASE V (W. U. D., A31551).—Mr. L. R., aged twenty-five years. Father died of tuberculosis (?). When six years old the patient fell on his head and was unconscious for a time. Attacks since twelve years of age accompanied by dryness of the mouth. Now has weekly attacks.

*Physical Examination.* Entirely normal. Blood-pressure, 108-60. Vision: O. D., 20-30; O. S., 20-19. Ophthalmoscopy negative. Mental age that of adult. No retardation. Blood Wassermann negative. Visual fields normal. Lateral stereoscopic plates of the skull: There is a peculiar circular shadow above

the outer orbital process of the frontal bone. The object lies outside the skull. Otherwise negative. Given posterior lobe extract (see Chart I) by hypodermic twice weekly for two months. During this period he had five severe and thirty-six light attacks. The extract of the whole gland and the desiccated whole gland were then administered for seven months, during which the patient gained fifteen pounds. However, there were fifteen severe and thirty-seven light seizures, so the treatment was stopped.

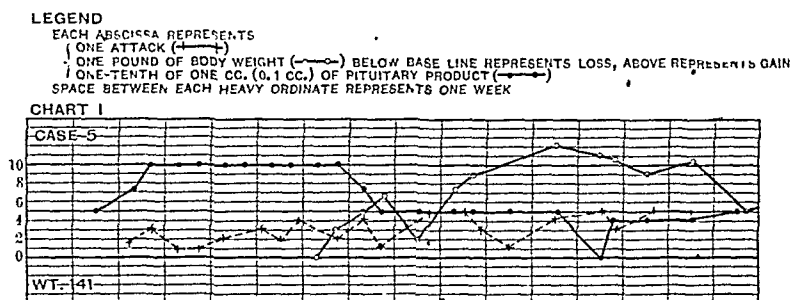


CHART I. Case 5.

CASE VI (W. U. D., A31684).—Mr. W. M., aged thirty-nine years, with a negative family and past history, has had epileptic convulsions for nine years not preceded by auræ. They occur at irregular intervals but are becoming more frequent.

*Physical Examination.* Several scars on head. Slight tremor of face. Teeth and gums in poor condition. Knee-jerk more active on the left. Other reflexes normal. Ophthalmoscopic examination showed normal fundi. Perimetry not done. Blood Wassermann negative. Mental tests showed a typical epileptic mentality with probably a primary mental defect. Scattering of tests, but good coöperation. Memory good for recent but poor for past events. Very emotional. Degeneration will be progressive and there is doubt of his ability to support his family. Lateral stereoscopic plates of the skull: Skull symmetrical, rather thin; sella rather small and its superior opening is very narrow. There are massive clinoid processes and calcification of the pineal body. Posterior lobe extract was given for three months followed by three weeks' administration of the extract of the whole gland, but there seemed no improvement, rather a more marked deterioration.

CASE VII (W. U. D., A16197).—Master L. S., aged sixteen years, had a normal family and past history. Has had monthly attacks for a year and a half. The convulsions are preceded by a severe headache, usually starting twenty-four hours before the attack.

*Physical Examination.* Left septal spur. Hypertrophied middle

turbinates. Small adenoid. Tonsils moderately enlarged. Visual fields normal. Vision of both eye 20-15. Ophthalmoscopy normal. Remainder of examination negative. Blood-pressure, 120-80. Blood Wassermann negative. Mental tests showed normal mental state with slight tendency to scattering. Extract of the posterior lobe was given hypodermically twice weekly for five and a half months (see Chart II), and the patient had no attacks. Following a visit to an exciting base-ball game he had four attacks resembling petit mal with no loss of consciousness. An episode of acute bronchitis resulted in a rapid loss of weight and five more attacks of a mild nature. A tonsillectomy was subsequently performed. The extract of the whole gland was substituted for four months, and there have been no ensuing attacks, but the patient has gained eight pounds in weight, or twenty pounds more than during his bronchitis four months before.

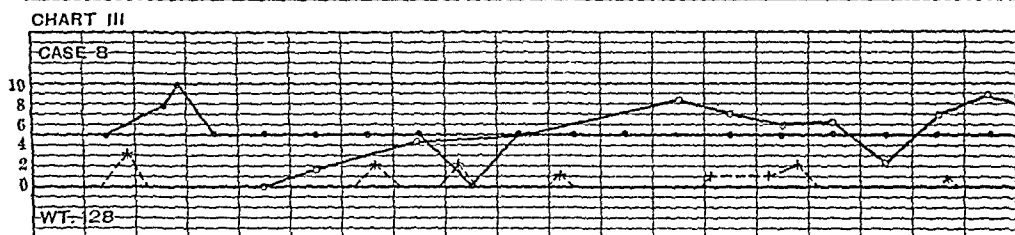
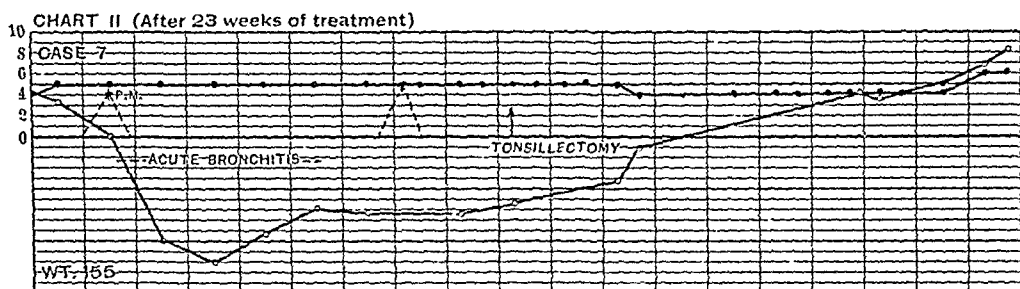


CHART II, Case 7.—After twenty-three weeks of treatment.  
CHART III, Case 8.

CASE VIII (W. U. D., 29784).—Miss M. M., aged eighteen years. Her father was an alcoholic and died during an "epileptic fit." Mother has had five or six abortions. Ten brothers and sisters died during infancy—cause unknown. Oldest brother has epilepsy and another brother has very severe headaches (migraine?). Patient's attacks began five years ago and now occur monthly or oftener. Has had enuresis nocturna since early childhood. Some swelling of the feet and ankles recently. Delayed, irregular menses.

*Physical Examination.* Short, sthenic type. Sparse axillary hair. Breasts rather large. No evidence of hypothyroidism. Reflexes normal throughout. Uterus small, in second degree of

retroversion, movable. Adnexa negative. Chronic endotracheitis. Cystoscopy showed a chronic trigonitis. Urine normal except a faint trace of albumin. Vision (both eyes), 20-15. Ophthalmoscopy, O. D., disk slightly pale, otherwise negative. O. S., disk normal. Perimetry disclosed a bilateral defect in the lower temporal field. Blood Wassermann negative. Mental tests normal. No deterioration or so-called epileptic constitution. Lateral stereoscopic plates of the skull: Skull generally thin; sella is small and the dorsum and posterior clinoid processes are bent forward and apparently bridge the fossa; the roof of the orbit and the great wings of the sphenoid approach the vertical; the frontal bone rises straight up anteriorly; the orbits are rather shallow (?). The diagnosis is suggestive of a mild degree of oxycephaly.

The administration of the posterior lobe extract was instituted for two months (see Chart III), followed by the exhibition of the whole gland (extract or desiccated) for six months, but numerous supervening attacks demonstrated the futility of further use of pituitary treatment despite the eight-pound gain in weight.

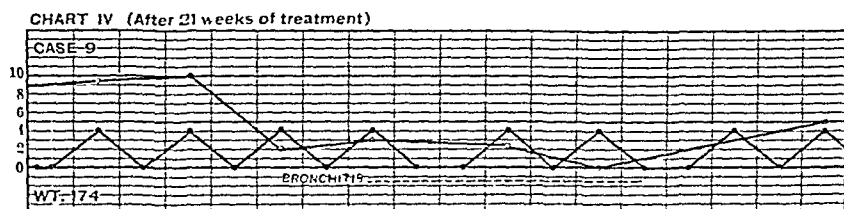


CHART IV, Case 9.—After twenty-one weeks of treatment.

CASE IX (W. U. D., A30683).—Mrs. M. Z., aged sixty years, whose family and past history were negative, has had convulsions for six or seven years, occurring every two or three weeks and preceded by vague feelings in the head. There is a definite history of polyuria, the patient claiming she passes three quarts of urine nightly.

*Physical Examination.* Facial aspect rather suggests an acromegalic, but there are no bony changes in the hands or feet. Ophthalmoscopy negative. Visual fields normal. Moderate emphysema. No arteriosclerosis. Blood-pressure, 100-70. Nervous system negative. Urine normal. Cystoscopy: Bladder negative; both ureters catheterized, negative; urine from both kidneys negative. Blood Wassermann negative. Mental tests show marked retardation that is not entirely accounted for by the language difficulty. No definite psychosis made out. Patient was given the extract of the posterior lobe for two months (see Chart IV) and three attacks occurred. The extract of the whole gland was then substituted and there have been no attacks in eight months.

CASE X (W. U. D., A14498).—Miss H. H., aged fourteen years. Father well. Mother has epilepsy and a positive (4 plus) Wassermann, and has had five spontaneous abortions. She has four children younger than the patient; one has "spasms." One child died of "marasmus." Present illness began a year ago, one week after an attack of "influenza." A second convulsion occurred four weeks later, and subsequently there have been attacks every two or three weeks. Tonsils and adenoids removed ten months ago.

*Physical Examination.* Thyroid slightly enlarged. No exophthalmos, tachycardia, tremor, etc. Further examination normal. Blood-pressure, 102-65. Vision (both eyes), 20-15. Ophthalmoscopy negative. Perimetry showed contracted fields for red and blue in the left eye. Right field normal. Lateral stereoscopic plates of skull negative. Both pituitary preparations were employed for four months, during which time there occurred thirteen severe and thirteen light attacks, although the weight remained almost constant. (see Chart V.)

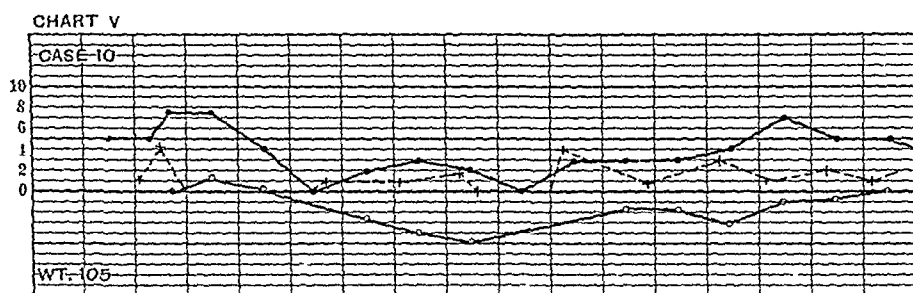


CHART V, Case 10.

CASE XI (W. U. D., A15143).—Mrs. C. R., aged forty-nine years. Married seven years. No pregnancies. Has had "typhoid fever" several times. "Nervous breakdown" seventeen years ago. Onset of convulsions three years ago. They now occur every month or two, but are not preceded by auræ. Frequent frontal headaches. Often has pain in epigastrium at no particular time of day. No relation to posture or food.

*Physical Examination.* Slight hypertrophy of the right inferior turbinate and more on the opposite side. Sinuses clear. Vision: O. D., 20-38; O. S., 20-30. Ophthalmoscopy negative. General examination negative. Gastric test meal normal. Sigmoidoscopy negative. Wassermann on blood negative. Mental tests showed normal reactions. Lateral stereoscopic plates of skull: Skull rather small; posterior fossa projects prominently downward and backward; otherwise negative. For four months the patient was given either of the two pituitary extracts. There were thirteen severe and twenty-five light attacks, while the weight decreased sixteen pounds.

CASE XII (W. U. D., 15324).—Mr. F. B., aged thirty-eight years, had a negative family and past history. Onset of epilepsy six years ago, with attacks of dizziness, but generalized convulsions did not occur until a year later. Seizures now once or twice weekly, sometimes once daily. Urinary frequency.

*Physical Examination.* Pupils rather small, equal and regular. React sluggishly to light. Accommodation reflex normal. Extrinsic ocular muscles negative. Heart showed slight general enlargement. Blood-pressure, 110-74.

Cystoscopy: Internal sphincter relaxed. Much tenderness in posterior urethra. Congested reddened trigone. No trabeculation. Ureteral orifices normal. Urine negative.

Vision (both eyes), 20-30. Ophthalmoscopy showed deep physiological excavation of disks. Perimetry showed normal fields.

Blood Wassermann twice negative. Mental tests showed characteristic epileptic constitution and marked mental deterioration. Deterioration will probably be progressive.

Lateral stereoscopic plates of skull: Skull contour very irregular and skull rather thin. The superior limit of the petrous portion of the temporal bone and the roof of the orbit are almost in a horizontal line, above which the clinoid processes project. There is an enormous increase in the size of the sphenoid sinuses. All other accessory sinuses seem enlarged. The sella turcica is very small and is bridged by the large clinoid processes.

The posterior lobe extract was administered for two months and although the patient gained eight pounds he had eleven severe and eight light attacks. During the previous year his average number of attacks under bromide treatment was for the same period nine severe and five light seizures.

CASE XIII (W. U. D., A32397).—Master H. H., aged thirteen years, had a negative family and past history. His first attack occurred a year ago, and he has had four subsequently.

*Physical Examination.* Small, active boy. Neurologically negative. External genitalia puerile in type. No pubic or axillary hair. Visual fields normal. Vision (both eyes), 20-15. Ophthalmoscopy negative. Mental tests normal. Patient is unusually bright. Wassermann on blood negative. Lateral stereoscopic plates of skull: Skull rather large, symmetrical; sella is small and shallow with large clinoid processes which approach each other. The patient was given extract of the posterior lobe for five months during which his weight remained constant and he had no attacks. Treatment was then discontinued. Four and a half months later his mother reported that he had had no further attacks and was growing taller and stouter.

CASE XIV (W. U. D., A33465).—Mr. B. B., aged thirty-two years, had been married twelve years and had four healthy children.

A sister, four years old, could not walk or talk, otherwise his family history was negative. Past history of no importance. Fourteen years ago the patient had his first attack and a second followed a year later. They now occur every three weeks and there are no auræ. Six months ago, for no reason known to him, there began a rapid increase in weight, forty pounds to date.

*Physical Examination.* Revealed a large, rather stout, but healthy appearing man. There was a fair hair distribution with an increase of adipose. Right pupil larger than the left. Both react well to light and accommodation. Neurologically normal. External genitalia normal. Vision (both eyes), 20-12. Ophthalmoscopy negative. Visual fields normal. Psychic study by Dr. B. C. Marshall showed normal behavior and good insight. Blood Wassermann negative. Lateral stereoscopic plates of the skull: A large hooked process at the external occipital protuberance, otherwise negative. The posterior lobe extract was given for a month followed by two weeks on the desiccated whole gland. As he had no attacks he discontinued further treatment. Seven and a half months later he reported having lost twenty pounds, but was in good health, although at times he became very nervous. There have been no further attacks.

CASE XV (W. U. D., A33339).—Miss V. R., aged thirteen years, who had a negative family and past history, has had for the past year and a half momentary spells, when her "mind seemed to leave her," although she was not dizzy and did not fall. First convulsion occurred eight months ago and there have been numerous ones since.

*Physical Examination.* Entirely negative. Vision (both eyes), 20-12. Ophthalmoscopy negative. Blood Wassermann negative. Mental examination showed no abnormal reactions. Mental age normal. Lateral stereoscopic plates of skull: Skull symmetrical; a slight degree of convolutional atrophy throughout; sella clearly defined and within the limit of normal dimensions. Diagnosis: Increased intracranial pressure. The patient was sent to the St. Louis Childrens' Hospital for further study. While there the spinal fluid was found to have a normal cell count and colloidal-gold curve. Wassermann on blood and spinal fluid negative. Von Pirquet negative. Complement-fixation for tuberculosis 2 plus. Another roentgen-ray examination of the skull suggested oxycephaly. There were no convulsions while in the hospital. The whole gland extract was administered for two and a half months and while she gained six pounds eight attacks occurred.

CASE XVI (W. U. D., A39768).—Miss R. C., aged seventeen years, had a negative family history. When four weeks old she had numerous convulsions and her life was despaired of. The attacks then ceased. Six years later there developed a right-sided paralysis



(hemiplegia?). Could not walk, talk or use the right arm. In six weeks she was able to walk. Since then she has always been nervous, but recovered from the paralysis. Nine years ago, during a thunder-storm, she had convulsions. Six months ago while abed with "influenza" she became unconscious. Since that time she has daily attacks which she describes as "choking in the throat." They occur two to six times daily, but there are no auræ or convulsions.

*Physical Examination.* Rather undeveloped. Does not appear her age. Small thyroid palpable. No pulsation, bruit, etc. Cold extremities. No dermatographism. Vision (both eyes), 20-19. Ophthalmoscopy negative. Visual fields normal. Mental tests: Grades up to a normal mental age level; marked memory defect both for numbers and words. Lateral stereoscopic plates of the skull: Skull long and not deep; sella small and shallow; very large dorsum sellæ and posterior clinoid processes; roofs of the orbit approach the vertical and join the inner table of the skull well up on the posterior aspect of the frontal sinuses; all accessory sinuses are large. Diagnosis: Indeterminate, suggestive of acromegaly of incomplete type.

The extracts of the posterior lobe and of the whole gland were given for two months. At the termination of that period the patient stated that the attacks are slightly less severe, although there is little change in their number. She feels much stronger, although there has been an intervening attack of mumps.

In analyzing the foregoing cases we attempted to use as criteria for study the following points:

1. Symptoms or physical signs referable to the hypophysis.
2. Abnormalities in mental reactions.
3. Roentgenographic changes in the sella turcica.
4. Fundus changes.
5. Abnormalities of the visual fields.
6. Body weight.
7. Number and character of the attacks.
8. General health of the patient.

1. *Symptoms or Physical Signs Referable to the Hypophysis.* Five cases (31 per cent of the total) displayed one or more features possibly ascribable to pituitary changes, and it is interesting to note that Tucker<sup>1</sup> in his larger series had the same incidence. The patients presenting these changes were (1) Case I, hypertrichosis of the chin and upper lip. (2) Case VIII, short, sthenic individual; abnormal fat distribution; sparse axillary hair (delayed, irregular menses) suggested an incomplete dystrophy adiposo genitalis. (3) Case IX, polyuria; acromegalic facies. (4) Case XIII, small stature; infantile genitalia; no pubic or axillary hair. (5) Case

<sup>1</sup> Tr. Sect. of Nerv. and Ment. Dis., Am. Med. Assn., 1919, p. 169, also Arch. Neurol. and Psychiat., 1919, 2, 192.

XIV, gain of forty pounds in six months; body contour and fat distribution suggested a hyposecretion of the posterior lobe.

2. *Abnormalities in Mental Reactions.* These were found in 6 cases (37 per cent) and varied from scattering of tests, retardation, memory defects, to marked mental deterioration. Three patients (19 per cent) showed what Dr. Smith terms a "typical epileptic constitution." He characterizes this group by their feeling of superiority, their superciliousness and diffidence. They are emotional, suspicious and irritable, and these differences are accentuated before attacks (see Cases I, VI and XII).

3. *Roentgenographic Changes in the Sella Turcica.* Discussion has been rife concerning the changes about the pituitary fossa demonstrable by the roentgen ray, and any consequent pressure or other effect on the contained gland. Johnston and his associates<sup>5, 6, 7</sup> claim that in essential (*i. e.*, "idiopathic") epilepsy there is a condition of "local acromegaly" characterized by large clinoid processes, roofing of the fossa, increased density of bony tissues forming the roof of the orbits, etc., and claim to have found one or more of these features in a very high percentage of cases. Timme<sup>8</sup> insists that roentgen-ray changes in the sella are not indicative of pituitary lesions, but claims that such a feature as "a closing in of the sella turcica" may be found. However, Munson and Shaw<sup>9</sup> think there are no constant changes in the pituitary gland from an anatomical point of view in these subjects, and the former author<sup>10</sup> as a result of autopsies on 85 epileptics at the Craig Colony draws the following conclusions: "The sellas from a series of unselected epileptic subjects present a wide variation in type. The average size seems a trifle smaller than the figures given for normals and the contained gland seems to weigh less. Roofing will be seen in the roentgenogram, but in reality the gland is well exposed and pressure seems a remote possibility. Bony changes are present but seem to be the anomalies which might well be present in a similar series of non-epileptic cases. There is no characteristic change to be seen in epileptic sellæ."

After these important observations by Munson it is noteworthy that 8 cases (50 per cent) in our series showed sellar changes (Cases I, III, VI, VII, VIII, XII, XIII, XVI), but that only 3 (Cases VII, XIII and XVI) improved under pituitary treatment. Two patients (Cases IX and XIV) who had unquestioned evidence of pituitary disturbance, and who did well under the gland administration, had roentgenographically normal sellæ.

<sup>5</sup> Am. Jour. Roentgenol., 1914, n.s., 1, 172.

<sup>6</sup> New York State Jour. Med., 1916, 16, 559.

<sup>7</sup> Pennsylvania Med. Jour., 1914-15, 18, 429. Also Jour. Nerv. and Ment. Dis., 1914, 41, 495.

<sup>8</sup> Arch. Neurol. and Psychiat., 1919, 2, 240; Arch. Ophth., 1920, 49, 268.

<sup>9</sup> Arch. Int. Med., 1914, 14, 393.

<sup>10</sup> Ibid., 1918, 21, 531.

4. *Fundus changes* were displayed by 3 patients (Cases II, III, VIII); 1 instance of slightly pale disks, 1 in whom the disk edges were blurred and irregular with pale retinæ and 1 case of bilateral optic atrophy.

5. *Abnormalities of the visual fields* were discovered in only 2 cases (VIII, X), 1 of whom showed a bilateral temporal defect and the other a unilateral contraction of the fields for red and blue. If, as is contended by Bell,<sup>11</sup> Cushing,<sup>12</sup> Engelbach and Tierney<sup>13</sup> and others, these "pituitary epilepsies" are due to pressure against the uncinate gyrus, it would seem rational to anticipate evidence of similar and coincident pressure on one or both of the optic nerves, probably at the chiasm, but the low evidence of changes in the fundi or visual fields, as found in this and other studies of epilepsy, would militate against such a hypothesis.

6. *Body Weight.* Numerous authors have noted loss of weight when pituitary gland was administered over long periods, some claiming that emaciation ensues. Bell<sup>14</sup> found that a few guinea-pigs gained weight during pituitary feeding and Burch<sup>15</sup> reports a patient who gained while taking the anterior lobe, but these findings are not correlated with other essential data or controls, and hence are of doubtful value.

In our series the weight curves presented wide variations, irrespective of the type of product employed, the increase or diminution in the number of attacks and without any dietary change by the patient. As a matter of fact there was a lower average gain by the cases that improved (0.77 pound per week) than in the unimproved patients (1.66 pounds per week).

Gain in weight . . . . .	6 cases (37 per cent) (Cases V, VII, VIII, IX, XII, XV)
Stationary . . . . .	5 cases (31 per cent) (Cases II, IV, X, XIII, XVI)
Loss . . . . .	4 cases (25 per cent) (Cases III, VI, XI, XIV)

The changes in weight were about evenly divided between the improved and unimproved cases, as follows:

Improved Cases: Gain, 2 cases (Cases VII, IX). Stationary, 2 cases (Cases XIII, XVI). Loss, 1 case (Case XIV). Gain per patient per week, 0.77 pound.

Unimproved Cases: Gain, 4 cases (Cases V, VIII, XII, XV). Stationary, 3 cases (Cases II, IV, X). Loss, 3 cases (Cases III, VI, XI). Gain per patient per week, 1.66 pounds.

7. *Number and Character of Attacks.* There seems to be considerable variance of opinion concerning the efficacy of pituitary treatment in stopping or diminishing the attacks. Clark<sup>16, 17</sup> and

<sup>11</sup> The Pituitary, 1919, Baillière, Tindall & Cox, London.

<sup>12</sup> Ibid., 1911, W. B. Saunders Co., Philadelphia.

<sup>13</sup> Medicine and Surgery, 1918, 2, 466 and 549.

<sup>14</sup> Loc. cit. The Pituitary, 1919, Baillière, Tindall & Cox, London.

<sup>15</sup> Journal-Lancet, Minneapolis, 1920, 40, 53.

<sup>16</sup> Jour. Am. Med. Assn., 1914, 63, 1652.

<sup>17</sup> New York Med. Jour., 1914, 99, 5.

Prior and Jones<sup>18</sup> report no success from this method of procedure. Timme<sup>19</sup> holds that feeding with the anterior lobe alone "produces marked improvement and even cures the disease" in many epileptics of the Froehlich dystrophy type; and Joughin<sup>20</sup> reports a case of this group. Tucker<sup>21, 22</sup> states that "good results with pituitary feeding need be expected only when the patient has some clinical evidence of hypopituitarism, and this should be backed by roentgenographical evidence."

How fallacious this line of reasoning is has been demonstrated by the fact that there were 5 cases (31 per cent) that improved definitely under treatment, and of this class 2 showed evidence of hypopituitarism and 2 others showed no roentgen-ray evidence of change in the sella turcica.

It was curious that none of our patients had so-called "uncinate attacks," and in fact few had any auræ, and none had auræ of an olfactory or gustatory nature.

The number and character of attacks in the unimproved cases were apparently not influenced by the treatment. In several instances there were more numerous seizures than when the patient had been under the influence of bromides, but there seemed no progressive increase as a result of the pituitary products, nor in any case was a change observed in the type of the attack. However, in several of the improved cases it is possible that the major fits alone were diminished. Thus Case XIV reports feeling "nervous" frequently, which may represent the equivalent of petit mal attacks, and Case XVI insists that while there seems no decrease in the number of attacks they are diminished in severity.

It might be apropos to state here that our experience with the amount of pituitary substance to be administered, while naturally varying with the size and age of the patient, has convinced us that in those cases amenable to this therapy much smaller doses (0.5 cc once or twice weekly) than are usually employed will prove sufficient. Conversely, in those patients not improved any amount of the gland may be used without more satisfactory results.

8. *General Health of the Patient.* This has proved of little prognostic value, for, as a rule, the patients did well under observation, and, as has been shown above, the average gain in weight was slightly greater for the unimproved cases than for those who were benefited by the treatment. Two of the improved cases developed attacks of acute bronchitis (see Charts II and IV) during the treatment, but despite a rather rapid loss in weight soon regained their previously augmented weight level.

<sup>18</sup> Jour. Ment. Sci., London, 1918, 64, 30.

<sup>19</sup> Arch. Neurol. and Psychiat., 1920, 3, 601.

<sup>20</sup> New York Med. Jour., 1916, 104, 693.

<sup>21</sup> Virginia Med. Semi-Monthly, 1916-17, 21, 1.

<sup>22</sup> Tr. Sect. of Nerv. and Ment. Dis., Am. Med. Assn., 1919, p. 169, also Arch. Neurol. and Psychiat., 1919, 2, 192.

**Conclusions.** While our comparatively small series of cases and the length of time they were kept under observation do not permit us to be dogmatic, the following conclusions seem justifiable:

1. Certain cases are apparently benefited by pituitary gland administration. In our series 5 cases, or 31 per cent.

2. The preferable product seems to be the extract of the whole gland, and the most satisfactory mode of treatment is hypodermically.

3. No cases showing the "typical epileptic constitution" were benefited.

4. There was no improvement in those patients with abnormalities of the fundi or visual fields.

5. Neither physical signs referable to the hypophysis, mental reactions (except the "typical epileptic constitution"), changes in the sella turcica demonstrable by the roentgen ray or variations in weight or health offered any criteria by which the relative degree of success or failure of the treatment could be predicted.

My thanks are due to Dr. Sidney I. Schwab for many helpful suggestions, and to Dr. G. B. Smith who performed most of the mental tests.

NOTE.—On account of the length of this article a number of the charts have been omitted.

## REVIEWS.

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THE CLINICAL STUDY AND TREATMENT OF SICK CHILDREN. By JOHN THOMSON, M.D., F.R.S.P. (EDIN.); Honorary Member, American Pediatric Society; Consulting Physician to the Royal Edinburgh Hospital for Sick Children; formerly Clinical Lecturer, Diseases of Children, University of Edinburgh. Third edition. Pp. 887; 249 illustrations. London: Oliver & Boyd, 1921.

THE third edition of this book has been enlarged to three times the size of the first edition. While covering the entire field of diseases of children the bulk of the text is devoted to clinical methods, clinical signs and symptoms and descriptions of those diseases which are either peculiar to children or show characteristics in children different from those occurring in adults. Little space is allotted to pathology, by which feature the author makes his work distinctive from the majority of books on the subject. By doing this he renders the book more attractive for those interested in the everyday treatment of sick children. The methods and diseases considered are those included in the ordinary conception of disorders of childhood, the subjects being arranged by chapters devoted to the diseases of the various anatomical systems. As a whole the subject-matter has been brought up to date as well as is possible, considering the many valuable contributions that are being made to pediatric knowledge constantly, and almost from day to day. Due to the time that must be devoted to the many processes incident to revision, it is understood that no book can be absolutely contemporaneous. Notwithstanding this allowance the occasion must be taken to specifically criticise the failure of any mention or allusion to the Schick test, which has been developed a sufficient number of years to warrant the addition of this method which has opened up avenues of prophylaxis and treatment of the greatest value. A. E. S.

SURGICAL CLINICS OF NORTH AMERICA, PHILADELPHIA NUMBER. VOL. I, NO. 1. By PHILADELPHIA CONTRIBUTORS, February, 1921. Philadelphia: W. B. Saunders Company, 1921.

THIS, the maiden number of the *Clinics*, sets a standard for the succeeding numbers. The work is published bimonthly and should meet with unqualified success, judging by this first example.

An introduction to the work is written by Dr. W. W. Keen, in which he briefly outlines medical and surgical advances since 1860. Following this are eleven contributions by some of the leading surgeons of Philadelphia, after the custom laid down by similar earlier works; most of the articles are transcriptions of a clinic. However, in many instances the writer has elaborated upon his subject and presented a striking monograph. Such an article is the one by Deaver on Pancreatitis; also J. G. Clark, C. H. Frazier, T. T. Thomas, and others, on special subjects.

These are the things that will appeal to the *Clinics'* readers, and it is to be hoped that the standard will be continued. The inclination is always present to give all the minutiae and details about isolated cases. This makes for voluminous and oftentimes irrelevant reading. These articles are singularly free from this fault and consequently are interesting, instructive contributions, well presented and full of meat.

E. L. E.

TEXT-BOOK OF TRACHEOBRONCHOSCOPY (TECHNICAL AND PRACTICAL). By SANITÄTSRAT DR. M. MANN. Translated by A. R. MOODIE, M.A., M.D., CH.B. (ST. ANDR.), F. R. C. S. (EDIN.), with 50 illustrations and 5 plates in the text, 10 colored plates in the Appendix. New York: William Wood & Co., 1921.

FROM the foreword of this book we quote the following: "Six years have elapsed since the appearance of the German edition of this book. No advances of importance have been made, either as regards the method itself or in its application." Is this an apology by the translator for having delayed so long in bringing this German work to the English-speaking otolaryngologist, or an indication of his attitude toward tracheobronchoscopy?

As a manual for the student or for the beginner in endoscopic work this book is scarcely adapted. The lack of detail in the chapter on anatomy and the comparatively small space given to technic presupposes more or less knowledge on the part of the reader. In the description of technic the author confines himself to the use of the Brunings's appliances, believing that these instruments are so superior to those of any other make that they are alone worth consideration. He does, however, give a fairly good history and description of a large number of the different tubes, forceps, applicators, and other instruments used in the various clinics of the world, especially those of Germany.

The second part, which is called "The Practice of Tracheobronchoscopy," occupies practically five-sixths of the text of the book, and consists of a careful review of the literature published up to the time of the appearance of the German edition, and is a systematically arranged compilation of abstracts. The illustrations of

the instruments are mostly from catalogues, with a few original photographs. There is also a series of colored plates which are interesting solely from a pathological standpoint, perhaps with one exception, where views through the bronchoscope are very accurately drawn and colored.

As an aid to those who are interested in the literature of the subject this book will be found very useful, but scarcely so for the student who desires to learn the practice of endoscopic manipulation.

G. B. W.

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TRANSACTIONS OF THE AMERICAN SURGICAL ASSOCIATION. VOL. XXXVIII. Pp. 709; illustrated. Philadelphia: William J. Dornan, 1920.

THIS volume of the *Transactions* contains the papers, forty-two in number, read before the Association at the meeting held May 3, 4 and 5, 1920. Several of these papers are on the subject of empyema and its treatment. These, taken with the free discussion, bring out some very useful and illuminating points. One other subject has more than one contributed paper, namely, the thyroid gland.

Every article is of first quality, and when written by men such as compose the American Surgical Association, we have a collection that is well worth not only reading but close study.

E. L. E.

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HISTORY OF THE PENNSYLVANIA HOSPITAL UNIT (BASE HOSPITAL No. 10, U. S. A.) IN THE GREAT WAR. Pp. 253, illustrated. New York: Paul B. Hoeber, 1921.

AN erstwhile historian records that when the British Army evacuated Philadelphia, in 1778, the military authorities carried off with them the bedding, instruments and medicines belonging to the Pennsylvania Hospital which they had been using for some two years. In this present record of returning good for evil we have a most interesting account of the services of a group of Pennsylvania Hospital men taking over a British base hospital at one of the Channel resorts and for nearly two years serving the sick and wounded of the English Army. The book portrays the details of organization, preparation, transport, the care of some fifty thousand sick and injured, the manifold activities about a base hospital in time of war, and the return home.

P. F. W.



**SURGICAL ASPECTS OF DYSENTERY.** By ZACHARY COPE, B. A., M.D., M.S., F.R.C.S., Surgeon to Bolingbroke Hospital, Hunterian Professor, R.C.S., etc. Pp. 157; 19 illustrations. London: Oxford University Press, 1920.

THE literature of the surgical aspects of dysentery is scanty, scattered and not readily available. This fact has led the author to collect the information and to supplement it with his own experiences of 2000 cases and the combined experience and information gained from others of much wider observations.

The subject is treated thoroughly, beginning with a chapter on pathology and its relation to the surgical complications. Differential diagnosis is discussed at some length, especially the question of recognizing the difference between an appendicitis and a dysenteric typhlitis or appendicitis. Amebic abscess of the liver is treated rather extensively in four chapters. Remote lesions such as iritis, parotitis, arthritis are all discussed.

E. L. E.

**KEEN'S SURGERY. VOLS. VII and VIII.** EDITED by W. W. KEEN, M.D., F. R. C. S., Emeritus Professor, Jefferson Medical College, Philadelphia. Pp. 1800; 996 illustrations, 29 of them in colors. Philadelphia and London: W. B. Saunders Company, 1921.

THESE two volumes contributed by surgical experts bring this great system up to date. They really are the great practical lessons of the War, put into organized form available for civil surgery and have added every worth-while achievement in surgery since the War. The very last word in surgical principles and practices is also included. The volumes are really a series of monographs by the masters of the various subjects discussed, and consequently the reader gets the very latest, best, most scientific and practical consideration of each and every subject. Then there is the added advantage that the editor has arranged, pruned and edited in the true sense of the word the entire composition.

A separate desk index volume to the entire work of eight volumes makes instantly available every detail on any subject.

It is throughout a most wonderful work—instructive, scientific, engrossing; at the same time most easy and pleasant reading because of the smooth style and diction.

E. L. E.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

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**Mobilization of the Elbow by Free Fascia Transplantation with Report of Thirty-one Cases.**—MACAUSLAND (*Surg., Gynec. and Obst.*, 1921, xxxiii, 223) says that ankylosis of the elbow results either from an infectious process or from traumatism. The latter is usually a fracture-dislocation with wide separation. The large amount of callus which forms as a result of this injury at first interferes mechanically with motion. Later an ankylosis results, usually fibrous in character. The infectious process may be either acute or chronic. The causative agent is usually the streptococcus, the pneumococcus, or the gonococcus. The onset is sudden and the course severe, ending usually in a bony ankylosis. On the other hand, the focus of infection is situated elsewhere, and the joint condition is caused by the hematogenous deposits in the joint either of attenuated bacteria or of toxins. The ankylosis results from adhesions within and without the joint and is, at least first, fibrous. In the elbow no position of ankylosis is favorable to function and any position is ungainly. No attempt at mobilization should be made until epiphyseal growth has ceased. Where the joint has been the seat of an infectious process, arthroplasty should not be done until all sign of active progress has ceased. As a rule one should not wait too long, as convalescence is lengthened where atrophy of the soft parts from disuse is marked. The operative technic is given. If there is no evidence of infection the cast should remain intact for a week. Passive movements are begun in ten days. The arm is always kept above a right angle. Gentle massage is instituted in three weeks, while baking is inaugurated after six weeks.

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**Gastric Operations.**—BARRINGTON-WARD (*Lancet*, August 20, 1921, p. 382) says that numerous theories of ulceration have been advanced—oral sepsis, embolism, intestinal stasis. The author gives at length the recent mechanical theory of Waugh—an abdomen in which the colon is abnormally mobile is a pathological abdomen and as such is more prone to pathological processes than the normal type. The abnormal

mobility is the predisposing cause. The exciting cause is the pull of bands and ligaments. Waugh has successfully treated formed ulcers of stomach and duodenum by colopexy only. The problem of dealing actively with the ulcer is still before us, for the majority of ulcers have progressed so far that natural repair cannot be expected. Gastro-enterostomy is a most valuable operation, but has been very much abused. The clear indications for its performance are: Gastric stasis due to organic obstruction of the stomach; an ulcer of the stomach or duodenum which may be afforded rest and allowed to heal by a short-circuiting of the food path. The absolute contraindication is an atonic dilated stomach. The author has found that the further from the cardiac end and the nearer to the duodenum the ulcer was situated the better were the final results. The final results of simple excision are disappointing and cannot be compared with those of partial gastrectomy, for excision has a higher mortality, is a difficult performance and often leaves a deformed hour-glass stomach. Partial gastrectomy has excellent final results. It removes an ulcer especially prone to malignant change. Two cases in the routine examination of the specimens showed early carcinoma. It is more certain to cure symptoms than gastro-enterostomy alone. The operation the author employed for partial gastrectomy is essentially the Billroth II method. Complete abdominal exploration was attempted in every case with special search for right iliac fossa abnormalities. The appendix was taken routinely. Cholecystectomy was done in three cases for gall-stones.

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**A Note on the Treatment of Secondary Hemorrhage from Branches of the Common Carotid Artery.**—BLAIR (*Ann. Surg.*, 1921, lxxiv, 373) says that secondary hemorrhage of the carotid artery and its branches is to be prevented by not suturing wounds that extend through the floor of the mouth and by packing or freely draining all wounds in the neck above the level of the thyroid cartilage that contain a ligated primary branch of the carotid artery. Secondary hemorrhage from a ligated primary branch might possibly be controlled by previously having placed the ligature as far from the carotid as possible and when bleeding actually occurs to free the stump from the surrounding indurated tissues and secondarily to ligate any branches that are given off proximal to this ligature and if necessary to loosely religate the stump itself as far from its origin as possible. If it is found necessary to place the ligature on the bleeding stump so close to the external carotid as to preclude the formation of a proximal clot, then the external carotid itself should be exposed and a ligature placed on each branch and on the trunk at least an inch from the bifurcation in the hope of establishing a permanent clot in the external carotid itself.

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**Gunshot Injuries to the Brain.**—SWANBERY (*Am. Jour. Roent.*, 1921, iii, 445) says that 3 of 11 cases reported died. Four cases had been operated upon, the foreign bodies removed. Three died from meningitis, giving an operative mortality of 75 per cent. Of the 8 living cases, 7 still have foreign bodies in the brain and 5 of these have Jacksonian epileptic attacks. The 1 patient who lived, following the removal of the foreign body has had no convulsions. All the cases except 1, however, complain of headaches or vertigo. About half the cases have paresthesia at times in the formerly para-

lyzed parts, although the paralysis itself has disappeared in most of the cases. The special symptoms are due to the traumatized portion of the brain through which the foreign body has passed to reach its final place.

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**The Value of the Various Methods of Bone Grafting Judged by 1930 Cases.**—McWILLIAMS (*Ann. Surg.*, 1921, lxxiv, 286) says that there are three requirements for a successful bone graft; bridging of the defect; size and type capable of reestablishing the circulation and stimulus to osteogenesis. The osteoperiosteal method offers a very large area of raw bone, hence it is to be preferred to all other methods of grafting. From a study of 1930 bone graftings the author concludes that the bony defect should be filled in with small bone chips and on one or two aspects, overlapping the ends of the fragments, covering in the bone chips, should be placed one or two strips of periosteum with adherent osseous plaques, taken from another bone. This method is applicable to large as to small bony defects. The cause of many non-successes is due to ineffective immobilization or to undue curtailment of its duration. From four to six months' immobilization is ordinarily required for complete success. There is sufficient evidence to prove that the most effectual treatment of non-union of fractures is bone-grafting. Despite some opinions to the contrary, bone-grafting should not be performed in infected fields. The causes of failure in bone graftings are improper methods of grafting, suppuration, insufficient immobilization, fracture and dislocation of the grafts, and atrophy of the ends of the bone to be grafted. The author states that the intramedullary method of grafting should be discarded.

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**Old Os Calcis Fractures.**—COTTON (*Ann. Surg.*, 1921, lxxiv, 294) says that os calcis fractures are of interest because they give so large a percentage of cripples and because these cripples are strong men as a rule in youth or vigorous middle age. The author judges that total disability for real work seems to be the fate of something like one-third to one-half the cases. He lays more emphasis upon remodelling than impaction for the resulting impaction is not mechanically first-rate as a rule. The treatment essentially has been developed with the idea of clearing away excess bone, on the outer side, removing spurs and limbering up joints by manipulation. The main features are similar in all the author's cases—shortened and flattened heel which is not touched in the repair measure; outward dislocation which calls for section of the calcis behind the post-astragular junction—spurs sometimes outgrowths from an original fragment, sometimes newly grown. They are removed very liberally as are all common osteophytic spurs. In the author's crippled cases the main pathology is the outward broadening due to the shoving outward of the peroneal plate of bone and to bone growth behind it associated with loss of some part of lateral motion constantly. The fracture is a crushing fracture with irregular cleavage lines and unusually massive bone replacement—a broad shapeless bone which has lost all chance of rocking under the astragalus. The key to the whole question is doing enough surgery. In his latter cases he has cleared away all excess bone deep below the cortical layer. In doing this clearing, he cuts across the post-astragular-calcaneal joint, regardless of ligaments and of joint capsule.

## PEDIATRICS

UNDER THE CHARGE OF

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**A Rapid Method for Determination of Water-soluble Vitamine B.**—BERMAN (*Jour. Am. Med. Assn.*, January 29, 1921) prepares the synthetic medium in which yeast cells are to be grown with and without the water-soluble vitamine B by adding saccharose 20 gm., ammonium sulphate 3 gm., calcium chloride 0.25 gm., potassium acid phosphate 3 gm., asparagin 3 gm. and magnesium sulphate 0.25 gm., to distilled water, and this solution is made up to 1 liter. This is then sterilized at 10 pounds' pressure and stored in the refrigerator. To 30 cm. of this synthetic medium in a graduate is added 1 c.c. of a Fleischmann yeast-cake measured and cut as 1 by 1 by 1 cm., and the whole is rubbed up with a glass rod until a complete and uniform suspension has been obtained. One-half of the suspension is then placed in the centrifuge tube graduated in tenths of a cubic centimeter and the other half is poured into a 15 c.c. centrifuge tube similarly graduated. To one is added a portion of the vitamine-containing solution, measured out into amounts of from 0.1 to 0.5 c.c. The tubes are then stoppered with non-absorbent cotton and incubated at body temperature. After twenty-four hours the cotton stoppers are withdrawn and the yeast cells thrown down in an ordinary centrifuge for a few minutes. An excess of growth will be found in the tube containing the vitamine and the reading can be compared with the control tube. As the amount of excess growth varies directly with the amount of vitamine a relative determination of this substance in the solution or in permanent uniform suspensions is practical. This relative value is called the vitamine B index, and it is obtained per cubic centimeter of solution by this equation: 
$$\frac{1}{\text{amount of vitamine solution}} \times \frac{\text{reading of vitamine tube}}{\text{reading of control tube}}$$
 It is necessary first to render the milk protein-free by the method of Osborne and Mendel.

**Stools and their Relation to the Feeding in Infants.**—GROVER (*Jour. Am. Med. Assn.*, February 5, 1921) recommends that the stools be examined in the napkins in which they are passed. He says that the high protein stool is the result of a small proportion of fat and a high proportion of protein in the food rather than too much protein, and is not a mark of indigestion. Its most characteristic feature is the shiny surface produced when the tongue depressor is passed through it. This shine must be differentiated from the glistening appearance of mucus, and also from the natural moisture of all freshly passed stools due to the water content. This type of stool is dull on the outside where the napkin touches it. The most typical high protein stools are produced from feedings of fat-free milk, undiluted and boiled hard

for three minutes. Besides showing the gloss they are very smooth when pressed out with the tongue depressor. They also appear to be transparent, the nap of the cloth being visible through the thin part of the stool. The stools are a shade of olive green. Soap in the stool is formed from the neutral fat taken by the baby which is broken down into fatty acids which readily unite with bases readily accessible in the intestine. The form of fat when absorbed by the intestine is soap and possibly also fatty acids. The intestine absorbs the most of the fatty acids and soap, but a small proportion passes out as a stool. If the fat in the formula is high and the protein is low there will result a typical soap stool, which is of very light color. They are usually dry and constipated and rarely average more than two a day. When spread out they appear smooth and dull. The granular soap stool differs from the normal soap stool in that the surface is granular when spread out with the stick. The granules are small masses of soap surrounded by mucus. They may be very minute or as large as pin-heads. The large granules are macroscopic but are also small fat curds surrounded by mucus. Starches in the stool are readily stained by the use of iodine or Lugol's solution. The particles of undigested starch stain blue or black. Stools containing much fermented starch are loose, acid, light brown, contain mucus and excoriate the buttocks. This type of stool is most likely to be found in babies having indigestion from certain of the proprietary foods. Indigestion of sugar presents no typical stool. They are frequent, very acid, excoriating and very watery. The solid parts are usually full of small air-bubbles formed by the chemical decomposition. These stools are usually green and those from maltose-dextrin preparations are usually brown, while those from sucrose or lactose fermentation are green.

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**Mental Disorders in Children Following Epidemic Encephalitis.**—LEAHY and SANDS (*Jour. Am. Med. Assn.*, February 5, 1921) report six cases varying in age from five to fourteen years. Of these four were boys and two girls. Their mental status was characterized by purposeless, impulsive motor acts, marked irritability, definite attention disorders, distractibility and changing variable mood, inadequate and inconsistent emotional reactions, marked insomnia, and in two cases precocious sexual feelings and intense eroticisms. The writers believed that these mental disorders can best be explained on a purely physical basis. While there was no pathological material upon which their opinion was based, reasoning by analogy from cases which showed similar lesions, such as are seen in true African sleeping sickness, in general paralysis and in subacute infections of the brain tissue, they arrived at this conclusion. The replacement of the destroyed tissue by neuroglia scar tissue acts as a stimulating and undoubtedly as an irritating agent to the rest of the nerve tissue. They further believe that the resolution of the mesodermic inflammatory reaction takes place over a relatively prolonged period and causes considerable irritation to the remaining relatively normal nerve cells. The irritation to the cell bodies results in the function of these cells with the production of the usual effects of the functions of such cells. There are, as a result, both sensory and motor disturbances and marked conduct disorder. The patients may be in the chronic stage of the disease, but this is prob-

ably not the case, because the patients physically showed no evidence of any disease process and all somatic manifestations of disease processes were absent.

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**Periodic Vomiting with Acetonemia.**—MARFAN (*Arch. de méd. des enf.*, January, 1921) says that the recurring attacks may occur at intervals of weeks, months or years and that there is no regularity about their occurrence. This condition was first described by Gruere in 1840, but the author claims that he was the first to call attention to the acetonemia in 1901. He pointed out a familial tendency and that this vomiting with acetonemia may occur in the course of some other malady and thus obscure the diagnosis. He claims that the primary cause is not in the alimentary tract but in some primary metabolic disturbance which causes the acetonemia. In the few cases that have come to autopsy the fatty degeneration of the liver and other signs of violent acute intoxication resembled those of chloroform poisoning. d'Oelsnitz found four children in one family with periodic vomiting with acetonemia. Two of these died in these attacks. The author himself had three patients who had been under observation for more than ten years who never had more than one typical attack. Between the ages of two and six the attacks are most frequent and most severe. After six years the frequency and intensity decline and the age of twelve years seems to be the final limit. Among sixty adults known to have had periodic vomiting with acetonemia in childhood four have attacks of migraine, two young women have had attacks of gall-stone colic after marriage and one man developed diabetes. During the attacks the urine contains large amounts of ketone bodies, but during the intervals the urine is normal. The attacks of vomiting may alternate with attacks of asthma or with transient fever or sometimes with somnolence with pronounced acetonemia or with convulsions, with stupor and sometimes with meningitic symptoms. One child of eighteen months developed convulsions after the attack of vomiting with somnolence or coma lasting for a week and leaving a flaccid paralysis for over a month. This child later had a recurrence of the vomiting with acetonemia.

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**Statistics on the von Pirquet Reaction.**—GITTINGS and DONNELLY (*Arch. Ped.*, February, 1921) reviewed twenty-seven cases found to be tuberculosis at autopsy. Sixteen of these had positive von Pirquet reactions and eleven had given negative reactions. They say that the clinical designation of generalized tuberculosis with meningitis depends upon the terminal meningeal infection. Generalized tuberculosis without meningitis usually is diagnosed as a pulmonary disease because of the extent of the pulmonary involvement. Since the tuberculin test is of clinical value only in the first year or two of life and the sputum is difficult to obtain there is justification of error. The distinction between infantile atrophy, chronic gastro-enteritis and non-tuberculous bronchopneumonia on the one hand and pulmonary tuberculosis on the other, may be extremely difficult in the presence of a negative tuberculin test. The margin of error should be reduced by repetition of the test. Unless the history and course be characteristic of the type the possibility of tuberculous spondylitis should always be considered in the

differential diagnosis of a spinal paralysis. This series demonstrates the high percentage of tuberculous infection and the comparatively low incidence of recognizable clinical tuberculosis in children. It is to be emphasized that there should be more than one repetition of the von Pirquet test if the first is negative.

## OBSTETRICS

UNDER THE CHARGE OF

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**Nitrous Oxid-oxygen Analgesia and Anesthesia in Normal Labor and Operative Obstetrics.**—DANFORTH (*Pennsylvania Med. Jour.*, March, 1921, p. 383) gives his experience in 1700 cases of labor in which nitrous oxide has been used. At the beginning of the second stage of labor the administration of gas is begun. In multiparæ it is usually begun a little before the beginning of the second stage, and this may be done with primiparæ who bear pain badly. A mask is placed over the face and the patient instructed to breathe deeply and rather quickly. Usually from three to eight respirations are needed to get the effect of the gas. In some instances gas is given throughout the length of the pain. If the anesthetist watches the patient it can readily be ascertained how many inhalations are needed to produce an effect, and this can be given throughout the labor. When once the patient feels the effect of the gas the mask can be removed and the relief from pain will continue throughout the length of the uterine contraction. It is important that the gas should be given immediately when the pain begins. If the pain becomes severe gas will not give complete relief. The percentage of oxygen added to nitrous oxide varies from five to fifteen, according to the necessity of each individual patient. The average percentage varies from five to eight. Before delivery patients do not rebreathe the gas. It is well to keep the patient under a condition of analgesia and not to let her pass into the anesthetic state. Should the latter be present struggling is much more likely to occur. If the proper percentage of oxygen is added cyanosis will be avoided. At the moment of expulsion it is well to add a small quantity of ether during the last three to five pains. This relaxes the muscles, decreases to some extent the violence of uterine action, which makes it more easy to control the passage of the head and prevent laceration. Under this episiotomy can readily be performed without inflicting pain. Just at the moment of expulsion the patient should be made completely unconscious with ether, from which she will quickly arouse. The administration of gas or ether is not a matter for an untrained person. Experience shows that analgesia is more difficult to secure and maintain than is anesthesia and that experience and training are necessary for both. When analgesia is properly produced it does not tend to lessen the vigor



or frequency of the pains; when anesthetics are skilfully administered during the second stage of labor the uterus often acts very vigorously and efficiently because relieved of the depressing influence of suffering. Consciousness need not be lost and the patient may assist very greatly by spontaneous effort. When the patient is nervous and excited and helping herself not at all the administration of gas often has a most happy effect. Even if the patient does not deliver herself, by its use she may carry on to the point where a simple forceps operation is all that may be needed. The use of gas during labor prevents exhaustion and patients recover very much more rapidly after confinement and with much less nervous prostration than if suffering is not relieved. The writer believes that the danger of postpartum hemorrhage is lessened by gas anesthesia. The uterine muscle is not relaxed as much under gas as where more complete anesthesia is obtained. In toxic cases it is thought of great advantage to avoid the irritating effects of ether and chloroform upon the organs of secretion. The writer has been unable to observe complications on the side of the child arising from the use of gas in labor. Cyanosis has been no more frequent than before gas was used. In reviewing a little over 530 labors there were 17 cases in which the child was lost. Nine died shortly after birth, eight were stillborn. Of the nine, six were premature, from six to eight months; one was one of a pair of twins and the other stillborn. One of the premature children born at seven months had also a cleft palate. Another living for a part of the day had a congenital heart lesion. Another had at birth an abdominal tumor, which turned out to be an enormously large bowel. Autopsy showed there was an obstruction of the sigmoid due to a peritoneal band caused by peritonitis which had occurred before birth. The mother had a severe attack of influenza during the pregnancy. In the case where pregnancy was complicated by a large fibroid in the lower uterine segment Cesarean section was performed, the child dying two days after birth from an unknown cause. This mother had no gas as the section was performed under ether. Among the stillborn children one had syphilis; another was one of a pair of premature twins—one was lost because the cord prolapsed, although version was done at once in the effort to save the child. There were two deaths among infants occurring in difficult high forceps delivery under ether, and there was one other fetal death, an anencephalic monster.

In operative obstetrics the problem is very different. Analgesia is rarely indicated, while surgical anesthesia is needed in all cases. Gas anesthesia is useful, when skilfully administered, in operative cases. It is not sufficient to give its administration into the hands of an obstetrical nurse untrained in anesthesia or some other untrained person. Even for surgical anesthesia the writer believes there is no anesthetic which is safer or more satisfactory within its proper field of use than nitrous oxide. When improperly given there is none more unsatisfactory and also to some extent dangerous. So far as apparatus is concerned none is perfectly satisfactory. None of these machines seem to be based on a knowledge of the physiology of the circulation and respiration. Under these conditions it is not strange that inexperienced persons often fail in producing good anesthesia. Primary perineal repair is probably the most frequent surgical operation in

obstetrics. Gas anesthesia is useful for this and rebreathing may be practised if necessary. A little ether may be added should occasion arise. It is sometimes difficult in these repair operations to keep the patient quiet because profound anesthesia is not needed, and with less the patient may become restless and struggling. Nitrous oxide allows the patient to wake with little or no nausea and does not tend to relax the uterus. In the low forceps operation anesthesia by gas has been found sufficient. If relaxation is not satisfactory ether may be added. The writer induces labor by means of a dilating bag. Nausea is usually avoided by using gas, especially if the patient is given no breakfast on the morning of the day in which the induction of labor begins. The writer uses bags to induce labor and would even give the patient analgesia for this manipulation. He believes that when a patient is perfectly conscious, if she has got self-control she can sometimes aid somewhat in this process. In incomplete abortion, curetting or packing may well be done under gas, and there is usually no difficulty in controlling the patient. For version the writer would rely upon ether, as considerable relaxation of the uterus is required. For Cesarean section the writer has used gas, with special success in eclamptic or toxic patients, as he believes the organs of elimination are less damaged than with ether or chloroform. Believing that an anesthetic which would dissolve fatty acids would injure a toxic patient the writer has used gas for some time. In this administration special care is necessary.

Cyanosis must be avoided, as otherwise the child will be injured, while the patient must be sufficiently asleep to permit manipulation. When the abdominal wall is completely relaxed there is danger that the bowel may be extruded. He does not believe that a preliminary injection of morphin is necessary in these cases, and he has found that the uterus contracts better during Cesarean section under gas than under ether. Cases in which the patient is in a very bad condition and in which the uterus must be quickly emptied are difficult to manage. Such an instance would be the pernicious vomiting of early gestation, where the patient is highly toxic. If the pregnancy is advanced to two and a half or three months the writer would perform anterior vaginal hysterotomy under gas, and has seen nothing but good results. The writer does not believe our methods of analgesia and anesthesia ideal, but his experience has shown that at present gas is a most valuable agent for some, at least, of the suffering which occurs in parturition. He believes that it injures the organs of elimination little if at all. He would not neglect methods of general attention, which often help the patient to bear the suffering of the first stage of labor. The value of morphin given by hypodermic injection has long been recognized. While the writer has had good results in the use of gas he does not believe that ether can be entirely discarded. Gas does not secure great muscular relaxation, and the attempt to do this will be followed by disappointment. Too much has been claimed for gas anesthesia and bad results have sometimes occurred. When gas does not obtain relaxation sufficiently ether must be added; and if a considerable quantity be required the results are not always satisfactory. The value of a skilled administrator cannot be overestimated. In discussion the point was brought out that just before the child is born it is well to give pure oxygen only for a few moments. This seems to avoid any tendency to cyanosis in the

infant. Respiration is established more slowly in the child after this procedure, but ultimately the child will breathe well. The same thing may be done in Cesarean section at the moment when the uterus is incised and the child delivered. So also patients who have received morphin before operation will benefit by pure oxygen. Cases of eclampsia are also benefited by this method. In forceps cases the operator must be careful not to begin traction with the forceps before the patient is completely relaxed. If the effort to extract the child is begun too soon no aid is secured from the uterus.

While the reviewer has had an experience similar to that of Danforth in many respects, he has also been led to believe that in highly toxic patients gas is a very dangerous remedy. In these patients the action of the heart is greatly disturbed and the second sound may be largely lessened or even abolished. Gas is sometimes rapidly fatal to such a patient. The safest anesthetic for use in all the requirements of obstetric practice is ether and oxygen. If these are combined by an experienced anesthetist the reviewer has seen no emergency in obstetric practice which could not safely be met by such anesthesia skilfully given.

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## GYNECOLOGY

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UNDER THE CHARGE OF

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**Radiotherapy of Fibroids.**—Until within the most recent past the treatment of fibroids has been exclusively surgical and the results achieved have been eminently satisfactory. Every decade has seen a material reduction in the mortality after operations for fibroids, but even in the hands of excellent surgeons there is yet an average mortality of from 3 to 5 per cent, and if we consider all the cases operated upon we would probably find a considerably higher percentage. Contrast with this the fact that radiotherapy has a mortality of zero. To be sure the word "cure" means something different in the two methods, according to GELLHORN (*Jour. Missouri State Med. Assn.*, 1921, xviii, 220), who calls attention to the fact that we obtain a cure after operation if we remove the fibroid and the patient survives and is well thereafter. In radiotherapy, on the other hand, we aim at only a *clinical* cure, that is to say, the object to be accomplished is attained, if the menorrhagia caused by the fibroid either ceases altogether or only a scanty or infrequent menstrual flow ensues. Furthermore a reduction in the size of the tumor is a part though not an essential one, of the clinical cure after radiotherapy. With these definitions in mind we

must approach the statistics thus far published. Many thousands of cases of fibroids have already been treated with radium or the roentgen rays, and the results obtained show on the whole a marked similarity. In order not to quote too many figures, the author mentions the collective statistics of 2982 cases of fibroids treated with the roentgen rays, in which there were 95.6 per cent cures and 4.4 per cent failures. In 944 fibroids treated with radium there were 94.4 per cent cures and 5.6 per cent failures. These statistics take into consideration the results obtained in various parts of the world, and they include the cases in which the technic had to be first acquired as well as those in which the technic had attained its present state of refinement. If only the latter kind were tabulated, Gauss and Friedrich found that in 425 fibroids roentgen-ray treatment yielded 98.4 per cent cures and had only 1.6 per cent failures, and exactly the same result was obtained in 372 fibroids treated with radium. It is important to remember that this type of treatment must not be given to fibroids which extend above the umbilicus. Large pedunculated subserous or submucous fibroids are likewise unsuited. In these three categories radiotherapy may produce a necrosis of the tumors. Cervical fibroids are refractory to radioactive treatment. Rapidly growing fibroids suggestive of sarcomatous degeneration, suppurating or gangrenous fibroids, or those in which any other form of degeneration has taken place, are to be operated upon, likewise those associated with carcinoma of the uterus. Fibroids pressing heavily upon the bladder or rectum had better be removed surgically. It is important, therefore, to carefully select the cases which are to be radiated, since the man who administers radiotherapy indiscriminately disregards the best interests of his patients as much as the man who adheres exclusively to surgery.

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**Observations on Ectopic Gestation.**—Any series of 307 cases of ectopic pregnancy must be of interest to the gynecologist but when, in addition to its size, such a series occurs in the practice of and is analyzed by such a surgeon as Polak (*Am. Jour. Obst. and Gynec.*, 1921, ii, 280), it must of necessity contain much of practical importance. His experience has shown that clinically all ectopics fall into two general classes: (1) Those which may be classed as in the non-tragic stage, with a pulse distinctly countable of 100 or under with a systolic pressure of 100 or over and a hemoglobin of 60 per cent or more. In this class there were 263 cases. (2) And those in the tragic stage pulseless at the wrist, with a blood pressure below 90, a hemoglobin under 50 and definite signs of internal hemorrhage and collapse. In this class there were 36 cases. The analysis of this series shows that ectopic pregnancy occurs most frequently where there is a congenital anomaly or a previous inflammation of the tube, in the woman who gives a history of premenstrual dysmenorrhea. Like other pregnancies, there is a period of amenorrhea or an attempt at menstrual suppression, but because of the unstable position of the ovum owing to the imperfectly developed tubal decidua and erosion of the ovum into the underlying muscle and venous radicles, bleeding takes place into the decidua and produces such ovular unrest as to cause tubal distention and peristalsis which is evidenced by colicky pains and uterine bleeding. The bleeding into the decidua plus the growing ovum distends the tube and causes the soreness and tenderness

over the region of the distended gestation sac. The relation of the physical signs to the pathology is still more striking and constant, as was shown by the study of this series. The uterus is enlarged, because it contains a deciduum which was prepared in anticipation for the reception of the ovum. This sign could be definitely demonstrated in all of the ectopic pregnancies of eight weeks or over. The cervix is soft, due to the congestion consequent upon pregnancy. This symptom is variable and is of no diagnostic importance. It was noted in a very few of the cases. Bimanual examination shows that the uterus does not have the usual characteristic diagnostic sign of pregnancy, *i. e.*, the elasticity of the median portion of the anterior wall and the compressibility of its isthmus. The absence of these changes in consistency is due to the absence of the growing ovum in the uterus, which though it is enlarged, is not changed in shape or consistency except for the slight softening of the cervix which is not constantly present. The cervix is exquisitely sensitive to motion. This is shown by palpation and is due to the peritoneal irritation from the blood which gravitates from the end of the tube or through the tubal wall because of its porosity and finally to the prolapse of the tubal mass into the cul-de-sac. This reaction of the peritoneum covering the utero-sacral ligaments makes them sensitive, hence anything which moves these sensitive bands will cause exquisite pain. This sign, pain on movement of the cervix, was present in all of the cases in this series. In considering the proper treatment of ectopic pregnancy, it should be remembered that primary rupture of the tube is not usually serious nor fatal. Less than 1 per cent bleed to death, 3 out of 307 cases in this series from the primary rupture, as the usual erosion goes through an arterial twig, and not the main vessel. Bleeding continues until the blood pressure falls, a clot forms and the bleeding ceases. The patient reacts, feels well for a day or two, and then a secondary rupture occurs and the doctor who has treated her for indigestion has missed the psychological moment to do the operation in the non-tragic stage. Polak's experience, and it has not been inconsiderable, teaches him that the best time to operate is after a reaction. This is shown by the slower pulse and gradual increase of blood pressure. Almost all of these patients will come back with rest and morphine. He gives them an initial dose of  $\frac{1}{2}$  grain and  $\frac{1}{4}$  grain every three hours, reducing the respirations to eight or twelve, and he has yet to see a case which has not reacted and become a safe operable risk under this treatment. No saline is used until after the operation, then never by infusion. Blood transfusion is preferable when the vessel has been tied, never before; but it is indicated during the procedure in severe cases. The operation consists in properly removing the tube without interfering with the collateral circulation of the ovary. This can only be done by individual ligation of the vessels in the mesosalpinx, not by mass ligation. After the tube is removed, the ovary is suspended by suture of the infundibulo-pelvic ligament to the round ligament and the raw surface at the top of the broad ligament peritonealized by whipping the mesosalpinx and round ligament together. It is only possible by waiting for reaction from shock to select the time for operation, then we can give the woman her best chance both as to mortality and morbidity.

## OPHTHALMOLOGY

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**Ocular Syphilis in the Second Generation.**—SIDLER-HUGUENIN (*Klin. Monatsbl. f. Augenhk.*, January, 1921, p. 44) discusses the question of the transmissibility of syphilis from grandparents to their grandchildren—a long-standing subject of controversy; the proof of such transmissibility is extremely difficult if Finger's requirements are to be satisfied, namely, (1) undoubted hereditary syphilis must be present in the first generation; (2) acquired syphilis in the father and mother of the first generation must be absolutely excluded; (3) the specific affections in the second generation must be indubitably of the form of inherited syphilis. The author considered it preferable, from the standpoint of practice, to limit his researches to an exhaustive examination of all the children born of parents clearly affected with hereditary syphilis; it is precisely in the domain of ophthalmology that the most certain results are attainable in the detection of hereditary syphilis (parenchymatous keratitis with 90 per cent of specific origin, typical alterations of the fundus). The author's material consisted of 250 cases encountered in the course of thirty years in the Children's Hospital of Zürich. Of these 250 cases he has been able to trace 50 couples, one of whose members belonged to the above 250 cases; 36 of these couples had children (only 65 all told) and 14 couples (28 per cent) had none. That the number of families belonging to the 250 cases above mentioned was so small is due to the fact that the subjects almost in their entirety belonged to the floating laboring population and that a precocious mortality of about 50 per cent exists in these cases; moreover, the survivors, frequently invalids, do not ordinarily marry and that their fecundity is very low. First, among the 50 couples, 27 (5 without children) mothers were affected with hereditary syphilis; these 22 couples had 44 children. Second, in the same series 23 fathers (9 sterile) were affected with hereditary syphilis; the entire number of children was 17; thus the genital apparatus in the male appears more vulnerable than in the female. The Wassermann was negative in all the children of both the above categories and the examination of the skeletons by the roentgen rays revealed but a single anomaly; the latter belonged to the first group. Among the anomalies *not strictly specific* the reporter found 2 cases of strabismus, 3 of rickets and 1 of tuberculosis; these dystrophies may as well be ascribed to faulty hygiene and defective alimentation. The one doubtful case is uncertain, for while the mother presented undoubted manifestations of hereditary syphilis, the father gave an uncertain Wassermann. Finger's postulate is accordingly not realized in this case. From these researches the high per-

centage of sterile marriages is very striking, particularly when it is the husband who is the subject of hereditary disease. Eight mothers at the time of conception and during the early months of pregnancy presented severe and indubitable signs of hereditary syphilis; their fourteen children showed no specific stigmata whatever. The author draws the conclusion that parents affected with hereditary syphilis will have none or few children, but that the latter will in all probability be healthy; nevertheless, when an individual affected with hereditary syphilis contemplates marriage it would be in order to subject him to energetic specific treatment prior to that event; if it be the prospective husband, there is absolutely no danger of the transmission of syphilis.

**The Eye of the Aged.**—MONAUNI (*Arch. d'ophthal.*, March, 1921, p. 180) contributes a study of the senile eye; the reporter concludes that such lesions may be reduced to the following types: Fatty and calcareous degeneration, decrease of the elastic elements and increase of hyaline substance. Fatty degeneration affects all the ocular tissues, especially the fibrous and vascular tunics as well as the refracting media; it attains its maximum in the sclera, the ciliary body and vitreous humor. Calcareous degeneration is more general in the posterior segment of the sclera, in the stroma of the ciliary body and in the vitreous, especially its anterior segment. The fats of the senile eye are, for the most part, constituted by cholesterin; to a less degree by the neutral fats. It is only in the vitreous bodies of the choroid that phosphatic compounds, saturated and non-saturated, are met with. The alterations of the elastic fibers consist in rarefaction of the elastic meshes, narrowing of the fibers and hyaline degeneration. Rarefaction and narrowing of the fibers affect all the ocular tissues as well as the optic nerve; these changes predominate in the cornea and sclera. In the cornea the anterior and posterior limiting membranes are affected with hyaline degeneration; the same is the case with the elastic fibers of the periphery, the choroidal vitreous lamina, capsule of the lens and very probably also the zonula and the large fibers of the vitreous body; the latter constantly show numerous crystals of variable chemical composition. In the explanation of the pathogeny of the *arcus senilis*, besides fat, account must be taken of the alterations of the elastic tissue of the periphery of the cornea, and especially also of hyaline degeneration. The vitreous bodies of the choroid must be regarded as hyaline productions of the vitreous lamina combined with the fats of the subepithelial layer of the choroid; there is present, in addition, a fatty degeneration combined, in all probability, with hyaline degenerations; the same is true of the fibers of the zonula and of the large fibers of the vitreous body; to these alterations is to be attributed the greatest importance in the pathogenesis of certain forms of luxation of the lens, senile synchysis and sparkling synchysis. There is the closest dependence between the lesions of the ocular membranes and those of the bloodvessels. The lesions above mentioned explain the disorders of nutrition and the ocular maladies of senility, as also of the disturbances of accommodation. Based upon the above findings, all more or less characteristic of arteriosclerosis, the writer concludes that the alterations of the senile eye are due, above all other causes, to atheroma; the appellation *cholesteric steatosis* of the senile eye, suggested by Vollaro, is quite suitable for the syndrome.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**The Value and Mechanism of the Colloidal-gold Test.**—After a comprehensive review of the colloidal-gold test, as applied to the examination of spinal fluid by Lange, CRUICKSHANK (*British Jour. Exper. Path.*, 1920, i, 71) detailed the findings of the gold sol, Wassermann and globulin in 27 cases of general paralysis, 1 of juvenile general paralysis, 3 of suspected general paralysis, 1 of taboparesis and 58 miscellaneous cases comprising different mental conditions, chronic dementia, epilepsy, dementia precox, delusional and other insanities. In the cases of general paralysis, the findings agreed with those of other observers in that all cases gave the paretic reaction, the Wassermann tests were positive and various degrees of globulin increase were detected in all instances. In the 57 cases representing various mental conditions, all gave negative Wassermann and gold reactions. As the reacting power of a syphilitic serum or spinal fluid had been shown to reside in the globulin fraction of the protein, paretic fluids were subjected to half saturated ammonium sulphate in order to get rid of albumen, dissolved in salt solution and dialyzed until free from salt. The precipitate of globulin was then dissolved in an amount of 0.8 cc of 5 per cent NaCl solution equivalent to the original volume of spinal fluid. It was found that the globulin had the precipitating power of the original spinal fluid, being even more active, and that the globulin gave positive Wassermann reactions. In 2 cases where the spinal fluid had yielded anomalous gold reactions, the separated globulin gave a paretic reaction in both instances. In this connection, it was learned by experimentation that the dialyzed albumen fraction acted as a protective colloid, which had apparently served to obscure the readings in the original fluid. The globulin from negative spinal fluids did not precipitate the colloidal gold, even in high concentrations, suggesting that the reactions of paretic fluids were not due solely to the increased content of globulin, but to an alteration in the physical or chemical character of the globulin and that the different zone reactions were dependent on the relative amounts of globulin and albumen, as suggested by Felton. The alteration in globulin cannot be regarded as specific for syphilis, since it occurs according to the work of others in multiple sclerosis, but it is interesting that the change is so constant in one and common in another, which is now suspected to be due to a spirochete, the author believing that only reaction of the paretic and luetic types should be regarded as a real diagnostic value and that meningitic reactions, while being of some value in conjunction with other findings



should for the present be held *sub judice*. He states that the reaction in syphilitic diseases of the central nervous system depends on a physical change in the globulin associated with increased positive electric charge.

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**Summary of Experimental Studies on the Histopathologic Changes Produced by Arsphenamine and Neoarsphenamine.**—The fatalities following the administration of arsphenamine and neoarsphenamine in the treatment of syphilis have usually been attributed to the toxicity of the drugs and to technical errors in administration referable to the preparation of the solutions and manner of injection. KOLMER and LUCKE (*Arch. Dermat. and Syph.*, 1920, ii, 289) studied the histopathologic changes produced in rats and rabbits by the intravenous injection of single large and multiple small doses of arsphenamine and neoarsphenamine. The animals were injected intravenously with acid solutions of arsphenamine, with single large (0.08 to 0.1 grams per kilo body weight) and multiple small (0.01 mg. per kilo) doses of solution of disodium arsphenamine. The single large dose corresponded to 4.8 and 6 grams for a person of about 130 pounds and the small dose to 0.6 gram per 130 pounds. From six to seventeen doses were administered. Neoarsphenamine was introduced into rats and rabbits in a single large (0.2 gram per kilo) and in multiple small doses (0.02 to 0.03 gram per kilo). The former corresponded to about 12 grams per 130 pounds and the latter to 1.2 to 1.8 grams per 130 pounds, from six to eighteen doses of the latter being administered. The histological study of the organs removed at necropsy showed that the lesions produced by neoarsphenamine were generally of the same character as those produced by arsphenamine but, in comparison with dosage, were less severe. Acid or non-neutralized solutions of arsphenamine produced several vascular injuries in all organs, characterized by congestion, hemorrhagic extravasations and the production of peculiar thrombi, with secondary cellular degeneration and necrosis. Single large doses of arsphenamine and neoarsphenamine also produced similar vascular changes, but in a milder degree; areas of focal necrosis and cellular degenerations in heart muscle, liver and spleen were rather prominent. The kidney lesions were composed of these vascular changes and varying degrees of tubular necrosis. Multiple small doses of arsphenamine and neoarsphenamine produced slight vascular changes of congestion and thrombi of conglutinated erythrocytes in the various organs; focal areas of cellular degenerations and necrosis were frequently well marked, particularly in heart and liver. The authors emphasize that the maximum changes were produced by large doses of acid solutions of arsphenamine and by doses of disodium arsphenamine and neoarsphenamine so large that they have no analogy to the amounts commonly administered to persons in one dose and at one time.

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**Dissemination of Spirocheta Pallida in Experimental Syphilis.**—With a view to confirm certain observations of earlier workers in the course of routine work in latent syphilis, and to throw some light on the behavior of certain strains which had been isolated from different sources, EBERSON (*Arch. Dermat. and Syph.*, 1921, iii, 111) performed experiments to determine roughly the presence of *Spirocheta pallida*

in the blood stream and regional lymphatic glands prior to manifestations of syphilis in the inoculated testicles of rabbits. It was found that *Spirocheta pallida* could be isolated from the blood stream of experimentally infected rabbits seven, ten and thirty days after intratesticular inoculation, at times corresponding to twenty-six, twenty-three and three days prior to the appearance of any initial lesions. Active, virulent *Spirocheta pallida* were found in the regional lymph glands of rabbits seven days after inoculation of the rabbit's testicle and twenty-six days before any primary lesion had appeared. The spleen was shown to contain *Spirocheta pallida* more than two months after the inoculated testicle had healed entirely and had been found free from spirochetes by repeated puncture and direct inoculation of the excised testicles in other rabbits. The author believes that for confirmation of experimental work and for diagnosis of suspicious syphilitic material which cannot be studied microscopically, the method suggested by these studies might be employed to advantage. He goes on to say that with early invasion of the lymph glands and blood stream established definitely during the incubation period of syphilis in animals, the theory of a life cycle of *Spirocheta pallida* is weakened; that the absence of organisms, as judged solely by microscopic findings, is not convincing proof that a change of form has taken place within the animal body and the fact that *Spirocheta pallida* have been found unaltered both in morphology and in virulence in the blood and glands would seem sufficient to render the theory untenable.

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**Variations in the Bacterial Flora of the Upper Air Passages in Course of the Common Cold.**—BLOOMFIELD (*Johns Hopkins Bull.*, 1921, xxxii, 362-121) presents a bacteriological study of common colds. A previous report of the normal anaërobic flora of the throat in healthy individuals was used as a control series. Cultures from the nasopharynx and tonsils of 10 cases were made during the active stage of coryza and during convalescence. It was found that in uncomplicated cases the flora differed in no fundamental way from that in healthy individuals. Just as in the normal controls, non-hemolytic streptococci and Gram-negative cocci were found to be constantly present, and there occurred a shifting transient flora of diphtheroids, coarse Gram-positive cocci, minute Gram-positive organisms, *Staphylococcus albus*, etc. However, this transient flora was richer and more varied than in the controls. The author suggests that the explanation of this is that the disturbances of the mucous membrane during the cold allows a general increased activity of bacterial growth, but none of these organisms can be the primary cause of the cold, because they are too variable and inconstant. He concludes that the etiological organism is unknown and is certainly not the streptococcus, which, however, acts as secondary invaders in local complications.

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**Experimental Production of Clinical Types of Syphilis in the Rabbit.**—Of late the tendency has been to lay more and more stress on the disease-producing properties of the organism concerned rather than the reactive mechanism of the host. The factors that determine these features of the disease may be numerous, and the results of their action differ so widely that diversity rather than uniformity has come to be

recognized as one of the most fundamental characteristics of syphilis. Inasmuch as the causes which underlie this diversity of clinical types are but little understood, BROWN and PEARCE (*Arch. Dermat. and Syph.*, 1921, iii, 254), utilizing a modified conception of the theory of inhibition, altered the defensive mechanism in different ways in order to produce types of disease that would conform to alterations in the mechanism of animal resistance, the infecting organism being maintained as a constant factor in the reaction. Forty-four rabbits were inoculated in the testes with the Nichols strain of *Spirocheta pallida*, using for each testicle 0.5 c.c. of an emulsion containing many spirochetes. In half the rabbits, both testes were inoculated. Each series was then divided into four groups. One group of 6 animals served as controls where the infection was permitted to progress without any interference. In a second group of 5 rabbits the testes were removed fourteen days after inoculation while in a third group, also of 5 rabbits, castration was performed twenty-eight days after inoculation. In the fourth group of 6 animals temporary therapeutic suppression of the testicular reaction was accomplished by a single intravenous injection of arsenophenylglycyl dichlor-m-aminophenol. All animals were observed for from three to three and a half months after inoculation. It was found that by early and radical interference (castration) it was possible to so alter the course of the disease as to cause bone lesions practically to supplant those of the testes in the defensive reaction, while, conversely, by permitting the testicular reaction to progress to a given point, it was possible to confer protection on this group of structures. In this case no bone lesions occurred but the generalized disease began with involvement of the next group of tissues in order, producing an infection essentially of skin, mucous membranes and eyes. It was also found that while in most animals inoculated in both testes a high degree of protection was seemingly conferred on other tissues in many instances, the protection failed to reach the eyes, lesions of the cornea and iris appearing as only clinical manifestations of a generalized disease—an observation which, as the authors suggest, might explain such conditions as neurosyphilis, in that certain tissues may fail to receive protection.

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ORIGINAL ARTICLES.

THE CAUSE AND THE CONTROL OF DYSPNEA IN DISEASE OF  
THE LUNGS.<sup>1</sup>

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DYSPNEA—difficult or labored breathing—occurs if the hydrogen ion content of the blood is raised and the subject is unable to increase his pulmonary ventilation promptly and adequately. With dyspnea one practically always finds hyperpnea, but the reverse does not necessarily follow. Dyspnea implies subjective discomfort. The hydrogen content of the blood may be raised by increase of (a) carbon dioxide and (b) lactic and other acids of metabolism. The role of anoxemia as a cause of dyspnea is of much less importance. Its effect is an indirect one through its influence upon the sensitivity of the respiratory center.

Pulmonary ventilation is so closely connected with cardiac efficiency that one has to consider this factor, even though one's thesis be limited to dyspnea due to disease of the respiratory organs.

*Orthopnea*, an exaggerated form of dyspnea in which the subject must sit up in order to get his breath, has been variously explained. It is generally assumed that the erect position is more comfortable because it favors the return of blood from the cerebral vessels and because it enlarges the thoracic cavity and increases the reserve air in the lungs, etc. Recently, however, since the relationship between

<sup>1</sup> Read before the American Climatological and Clinical Association, June, 1921.  
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anoxemia and shallow breathing has been pointed out,<sup>2</sup> it appears not unlikely that an erect position is chiefly beneficial because it minimizes uneven ventilation of the lungs.

Among the factors which will require special consideration are (1) the dead space; (2) pulmonary ventilation; (3) lung volume.

**I. The Dead Space.** By this we understand the whole of the respiratory passages into which air is inhaled during respiration excepting the alveoli of the lung—nose, mouth, trachea, bronchi, etc. During shallow breathing the dead space is relatively large; during deep breathing it is small. The dead space varies not only relatively, but actual variation may be brought about by changes in the size of the infundibula (Hoover). It is also interesting to note that the dead space for oxygen is larger than that for carbon dioxide, a difference which is probably due to the fact that considerable quantities of CO<sub>2</sub> may diffuse out of the bloodvessels in the walls of the respiratory channels. However, the dead space is essentially physiological rather than an anatomical conception. "The magnitude of the space depends on the physiological efficiency of the respiratory surface in relation to the supply of venous blood and fresh air" (Haldane).

While there is still no unanimity of opinion on the subject, the normal dead space for resting subjects is generally accepted as lying between 120 and 140 cc. Some investigators found the dead space much larger during deep breathing, though Pearce found but little difference. According to Krogh and Lindhard, maximal pulmonary inflation may increase the dead space by 100 cc.

But the dead space may also be increased by involvement of the pulmonary parenchyma. Thus if the alveoli of one lobe or one lung cease to functionate as a result of pulmonary consolidation or circulatory disturbance an increased dead space results. Again, edema of the lungs or exudate in the bronchi not only increases the dead space but also decreases the pulmonary ventilation. Further, if the dead space is large increase in ventilation may accomplish but little.

**II. Pulmonary Ventilation.** By pulmonary ventilation one understands the total amount of air which enters and leaves the lungs. If one assumes that the dead space for a given subject is variable, pulmonary ventilation is not synonymous with alveolar ventilation. Pulmonary ventilation is regulated by the medullary respiratory center, which is in turn affected by (a) afferent nervous stimuli and chiefly through the vagus and by (b) chemical factors.

The respiratory center may vary in its threshold of response. Thus caffeine and anoxemia are supposed to increase and opium and certain toxins to decrease its irritability.

Of far greater importance, however, is the hydrogen ion concentra-

<sup>2</sup> Haldane, Meakins and Priestley: Jour. Physiol., 1919, 52, 433.

tion of the blood, a very small increase of which produces an immediate response on the part of the respiratory center. Thus any increase in the  $\text{CO}_2$  tension of the blood promptly increases the respirations, whereas forced deep breathing, which depletes the blood of  $\text{CO}_2$ , is followed almost invariably by apnea (acapnia). Other acids in the blood, such as those which occur in the acidosis of diabetes, have a similar stimulating effect.

**III: Lung Volume.** The term *vital capacity* is applied to the maximum quantity of air which can be forced out of the lungs after a forced maximal inspiration. The air still remaining in the lungs is known as residual air, and these two factors combined constitute the total lung capacity. The air which enters and leaves the lung during quiet breathing is called the tidal air and the pulmonary capacity at the middle of such quiet breathing is known as the midcapacity.

All of the foregoing factors are subject to individual and temporal variation. Thus midcapacity is increased by a change of posture from the recumbent to the erect position. It is also increased by dyspnea, high altitude and exposure to cold.

Exercise may enormously increase pulmonary ventilation, the reserve factor of safety being estimated at 90 per cent as compared to 13 per cent usually accredited to the normal heart. As a rule, pulmonary volume decreases promptly after cessation from exertion, although it may persist for one or two days. Pulmonary volume has been found increased in the players of wind instruments and in glass-blowers (Hewlett).

Pathological pulmonary distention accompanies stenosis of the respiratory passages, and it may be a local phenomena if the bronchus of a given lobe or part of a lobe is constricted.

Asthma usually causes great pulmonary distention. Sometimes this disappears within a few days, but often, especially with recurrent paroxysms, it tends to remain more or less permanently.

**DYSPNEA AND CYANOSIS.** It may not be amiss at this stage of our discussion to point out certain facts regarding dyspnea and cyanosis. It is well known that a patient may have marked air hunger and yet not be cyanotic, and, on the contrary, he may be quite blue without dyspnea. Thus a patulous cardiac septum permits a mixture of venous with arterial blood and accounts for cyanosis, but an intact alveolar surface eliminates sufficient carbon dioxide and hence dyspnea is absent. But let such a patient develop an edema of the lungs which interferes with carbon dioxide elimination and he becomes dyspneic at once. As Hoover has pointed out, this occurs in pulmonary edema from other causes. The frothy exudate in the bronchi if saturated by breathing pure oxygen becomes after a few minutes an oxygen foam and diminishes cyanosis. The carbon dioxide, meanwhile, is not carried off and dyspnea continues.

Again, in pneumonia a whole lung may be solidified, take up no oxygen, and thus as long as circulation in this lung continues, contribute venous blood to the arterial stream, thus causing cyanosis. The sound lung, however, is still able to eliminate sufficient carbon dioxide to prevent dyspnea. But let the sound lung become edematous and dyspnea appears.<sup>3</sup>

A large pleural effusion may throw one lung completely out of commission and yet no cyanosis may be present, because the completeness of the atelectasis shuts off the blood supply and hence no venous blood reaches the arterial stream.

Again, in chronic pulmonary tuberculosis there may be the most extensive pulmonary involvement with dyspnea but without cyanosis, because, again, the blood circulation is cut off at the same time as the alveolar function (Hoover).

It is perhaps unnecessary to recall the fact that anoxemia causes in the main a shallow and rapid respiration, whereas excess of carbon dioxide produces deep respirations. Cyanosis always indicates anoxemia, the hemoglobin being more or less reduced in quality, but anoxemia does not necessitate cyanosis. "In carbonic-oxide poisoning the blood is cherry red, and yet the patient may die for want of oxygen. Again, when carbonic acid is deficient the tissues may be suffering from anoxemia, and yet the blood may be red with hemoglobin, which will not part with its oxygen (according to Bohr's law) because of the lowness of the  $\text{CO}_2$ " (Rudolf).<sup>4</sup>

It must also be remembered that oxygen is carried to the tissues not only by the corpuscles but also by the plasma, and that the plasma content of oxygen can be greatly increased by raising the oxygen content of the respired air. This is one of the facts which helps to validate oxygen therapy.

Inhalation of pure oxygen by animals over prolonged intervals of time may be sufficiently irritating to set up a pneumonia. But as used clinically in human beings no such irritative action need be feared.

**PNEUMONIA.** Dyspnea in pneumonia may result from (1) pain, (2) extensive consolidation, (3) excessive bronchial secretions, (4) edema (usually cardiac) of the uninflamed alveoli, (5) pleural or pericardial effusion, (6) acidosis.

The conditions here are diametrically opposed to those encountered in late chronic pulmonary tuberculosis. In the latter instance the alveolar surface is gradually lost and the circulation in the involved portions is simultaneously occluded. Hence, the respiratory center accustoms itself to the gradual increase in the carbon dioxide tension of the blood, and, further, but little or no venous blood is contributed to the left heart by the lungs. In pneumonia the respiratory and circulatory mechanism is subjected to great

<sup>3</sup> Pearce, R. G.: *Tr. Assn. Am. Phys.*, 1917, 32, 71.

<sup>4</sup> *AM. JOUR. MED. SCI.*, 1920, 160, 10.

and sudden abnormality,  $\text{CO}_2$  tension is suddenly increased and unaërated blood passes from the diseased lung into the general circulation. The circulation of blood through the lung seems to vary with the stage of inflammation. During red hepatization it is, as a rule, fairly well preserved, but during gray hepatization most of the smaller arteries are occluded (Gross).

The respiratory center in pneumonia is depressed through a peripheral vagus mechanism,<sup>5</sup> its threshold of stimulation to carbon dioxide being less than normal. Hence, as shown by Pearce,<sup>6</sup> the carbon dioxide of the venous blood may be increased, although the alveolar carbon dioxide and the blood carbonates may be practically normal.

It has been suggested that the cyanosis of late pneumococcus pneumonia may sometimes be due to methemoglobinemia,<sup>7</sup> but Stadie's<sup>8</sup> investigations have shown that the degree of arterial and venous oxygen unsaturation varies greatly and that its amount is proportionate to the degree of cyanosis present. Further, that no unusually low total oxygen capacities are encountered even in fatal and intensely cyanotic cases, and hence no great degree of methemoglobinemia can exist. But inasmuch as most of his cases were of the influenzal type the possibility of methemoglobinemia as a cause of cyanosis in typical pneumococcus lobar pneumonia cannot be altogether denied.

Acidosis is another possible cause for dyspnea in pneumonia. As in other infections a mild degree of acidosis from metabolic changes may exist, but in addition it has been shown that acid production is an important bactericidal factor in the growth and death of the pneumococcus.<sup>9</sup> Hence, one wonders whether such acid production may be sufficient to alter the hydrogen ion content of the blood in sufficient degree to stimulate the respiratory center. During the febrile stage evidences of acidosis are often demonstrable by "increased ammonia and acid excretion, low carbon dioxide tension of the blood, diminished affinity of the blood for oxygen and the retention of large amounts of alkali." Peabody<sup>10</sup> found diminished carbon dioxide tension of the blood and Palmer and Henderson<sup>11</sup> increased ammonia and titratable acidity of the urine as well as increased alkali tolerance. However, Palmer's<sup>12</sup> investigations of pneumonia acidosis, as measured by the combined carbon dioxide in the plasma and the hydrogen ion concentration of the urine, indicate that such acidosis is seldom if ever severe. Hence, direct treatment of acidosis is rarely if ever necessary.

<sup>5</sup> Porter and Newburgh: *Am. Jour. Physiol.*, 1917, 42, 175.

<sup>6</sup> *Tr. Assn. Am. Phys.*, 1917, 32, 71.

<sup>7</sup> Butterfield and Peabody: *Jour. Exper. Med.*, 1913, 17, 97.

<sup>8</sup> *Ibid.*, 1919, 30, 215.

<sup>9</sup> Lord and Nye: *Ibid.*, 389.

<sup>10</sup> *Ibid.*, 1912, 16, 701.

<sup>11</sup> *Arch. Int. Med.*, 1913, 12, 153.

<sup>12</sup> *Jour. Exper. Med.*, 1917, 26, 495.



*Pain* is in large manner responsible for shallow breathing, and this, as has been shown by Meakins,<sup>13</sup> may be an important cause of anoxemia. In these investigations it was found that with increasing respiratory rate there was a decrease in volume per respiration, but that the total minute volume was increased. There was, however, a "conspicuous diminution in the ratio between the volume of each respiration and the theoretical dead space." In other words, although the patient is breathing hard, pulmonary ventilation is poor. Here, too, a vicious circle may be established. Anoxemia produces shallow breathing and shallow breathing increases anoxemia. It is highly important, therefore, for this reason, as well as on account of the suffering and loss of sleep which it entails, to control pleuritic pain.

Pain is to be relieved by strapping, opiates, dry cupping or an ice-bag. The latter is often inadvisable in children, in the aged and in asthenic cases. We may also properly consider the fact that it may reduce temperature and that fever seems to bear a close, though as yet imperfectly understood, relation to the processes of immunization by virtue of which the crisis is induced. Some authorities bar the ice-bag for this reason even though its actual effect upon the reduction of temperature appears to be almost negligible.

*Extensive consolidation* as a cause of dyspnea is less easily combated. In sthenic cases, with a high venous pressure, phlebotomy is often advisable and cardiac stimulation indicated, digitalis being usually the most satisfactory drug. A copious supply of fresh air is essential.

*Excessive secretions* in the bronchi may result from concomitant bronchitis or from pulmonary edema. In the former instance aromatic spirits of ammonia or kindred drugs are useful; in the latter, digitalis and atropin are of proved merit, while epinephrin may be tried, especially if bronchial spasm be a contributing factor.

*Pulmonary edema* is a common late manifestation, not necessarily of marked and easily demonstrable degree, but simply as an excess of alveolar moisture which interferes to a greater or less extent with pulmonary ventilation by increasing the dead space.

Here, again, chief reliance must be placed upon digitalis and atropin, while phlebotomy and dry cupping may be considered. Massive *pleural* or *pericardial effusions* should be aspirated if edema threatens, or if by their size they interfere with pulmonary ventilation or heart action. In any of the foregoing conditions oxygen inhalation may be advisable. It is always indicated if anoxemia exists, and, as already stated, cyanosis always indicates anoxemia. The use of oxygen, as lately emphasized by Rudolf,<sup>14</sup> is certainly rational and has the forceful endorsement of no less an authority

<sup>13</sup> Arch. Int. Med., January 15, 1920.

<sup>14</sup> The Therapeutic Use of Oxygen, AM. JOUR. MED. SCI., 1920, 160, 10.

than Haldane, from whom I quote: "It may be argued that such measures as the administration of oxygen are at the best only palliative and of no use, since they do not remove the cause of the pathological conditions. As a physiologist I cannot agree with this reasoning. The living body is no machine, but constantly tending to maintain or to revert to the normal, and the respite afforded by such measures as the temporary administration of oxygen is not wasted but utilized for recuperation." But to be efficacious it must be properly administered, not by means of a funnel held near the patient's mouth, but by means of a rubber tube inserted into the nostril. Even its intermittent employment may spare the respiratory center as well as the other bodily tissues from the evil effects of anoxemia. The generally accepted teaching that pneumonia patients should be kept recumbent is usually correct; but occasionally obese patients with a more or less emphysema or those with cardiac lesions are much less dyspneic when propped up in bed.

**BRONCHIAL ASTHMA.** Obstruction to expiration is greater than to inspiration. This increases the midcapacity and produces pulmonary distention. The diaphragm is forced down, which may interfere with the blood flow through the inferior vena cava. Diminished diaphragmatic excursion still further favors venous and lymphatic stasis. The amount of air breathed during an attack may actually be increased, but the dead space is also increased and hence little is gained by the added effort. Cyanosis indicates the degree of anoxemia. The spasm of the bronchioles and increased secretion are probably the results of a vagus stimulus. It has been suggested that the nervous center governing the bronchial muscles is hyperesthetic.

Asthmatic attacks are best controlled by epinephrin, atropin, morphin and benzyl benzoate. Counterirritation on the chest, neck or feet may be a useful adjuvant.

Recurrence may be prevented by the elimination of reflex causes, especially pathological conditions in the nose and pharynx.

Anaphylactic asthma may be cured if the offending antigen can be discovered. Hay fever asthma can be prevented if the proper pollen extract is administered. The rarer forms of anaphylactic asthma due to certain varieties of food are sometimes prevented by discovery and withdrawal of the particular protein in question. So also may those due to bacterial proteins by means of appropriate autogenous vaccines. In my experience, however, the results obtained from the last-mentioned two varieties have been discouraging.

In many cases no specific cause can be determined. It is only fair to state, however, that in many of these cases complicating factors, such as chronic pulmonary emphysema and fibrosis, anthracosis, arteriosclerosis, etc., have played a part.

EMPHYSEMA. In this condition pulmonary overdistention is usual and marked. One finds an increase in the midcapacity and an inability to properly ventilate the lungs, the residual air being increased. According to Bohr,<sup>15</sup> increase in the midcapacity in emphysema is essentially compensatory and facilitates circulation through the lungs. These views regarding the importance of physiological and pathological variations in the midcapacity have not been generally accepted. Diminution of the residual air, however, is of unquestioned importance and points toward a diminution of the alveolar surface. The vital capacity is decreased and the dead space increased. The increase of the dead space is not admitted by all observers. R. G. Pearce<sup>16</sup> attributes the high CO<sub>2</sub> figures to instrumental error and explains the cyanosis as resulting from a low oxygen content of the blood. According to this conception the low O<sub>2</sub> content of the diseased alveoli is not compensated by over-ventilation of the sound alveoli, because superventilation will not increase above the normal the absorption of O<sub>2</sub>. Hence the oxygen tension in the blood leaving the heart will be low. The latter factor may be further magnified by the presence of moisture in the alveoli and the bronchi. This factor is indeed often the only one which is amenable to treatment. One cannot restore damaged alveoli nor their narrowed capillaries. It should be remembered also that the emphysematous subject not only requires more tidal air than a normal subject, but that the act of breathing itself is often so laborious that much carbon dioxide is thus produced. Further, that it is often impossible for him to increase his respiratory rate. The carbon dioxide tension in the alveolar air is abnormally high. The increased carbon dioxide content of the blood does not, however, produce its characteristic symptoms and sequelæ as promptly or at as low concentrations as it does in normal persons. This increased CO<sub>2</sub> tolerance by the emphysematous subject is in part due to an obtunding of the respiratory center and in part due to an increased value of the buffer substances in the body fluids (Scott).<sup>17</sup>

But little can be accomplished in controlling the dyspnea of emphysema. That moiety of the total which is due to asthma, bronchitis, edema or passive congestion may be amenable to treatment. Hence, digitalis, expectorants or atropin may be of value, as may also a change of climate. Hoover suggests that in emphysema with bronchitis, if cyanosis exists, but disappears under the inhalation of pure oxygen, we are justified in assuming that the anoxemia is the result of moisture in the air spaces and hence should expect beneficial results from a dry climate. If the patient remains unbenefited by the oxygen he will probably also remain unimproved

<sup>15</sup> *Deutsch. Arch. f. klin. Med.*, 1907, 88, 385.

<sup>16</sup> *Physiology and Biochemistry in Modern Medicine*, 1918, 311.

<sup>17</sup> *Observations on the Pathological Physiology of Chronic Pulmonary Emphysema*, *Arch. Int. Med.*, 1920, 26, 544.

by a dry atmosphere. Clinically it is common to find emphysematous individuals made worse by a visit to the seashore and improved by a trip to the mountains. Any factors tending to produce an acidosis should be vigorously combated, for the reasons already stated.

**PULMONARY TUBERCULOSIS.** In early pulmonary tuberculosis the total and midcapacity of the lungs is usually normal while residual air may be increased. In moderately advanced and advanced cases the total capacity and midcapacity are decreased and residual air normal or increased. Dyspnea in this condition rarely calls for direct treatment except in the event of complications, such as massive effusions into the serous cavities or pneumothorax. These conditions will be considered elsewhere.

In advanced chronic cases, dyspnea, except upon exertion, is a late manifestation which usually results from widespread destruction of alveolar function. This is of such gradual occurrence and associated with coextensive and simultaneous obliteration of the pulmonary circulation that one is often surprised at autopsy to find how little sound tissue remains. Experimentally, one-sixth of the total lung volume is compatible with life as long as the animal remains at rest. In autopsies on tuberculous subjects what appears to be an equivalent destruction of tissue is often found. Dyspnea in advanced cases may result from coincident bronchitis, and when so may be relieved by appropriate treatment. Theoretically, heart weakness with passive pulmonary congestion may be a factor, but practically it rarely is so and digitalis medication is usually productive of little benefit. In the advanced cases some opiate gives the best results.

Pain resulting from pleurisy, by causing shallow breathing and increasing the dead space, may be a cause of dyspnea. This subject has already been discussed under the heading of Pneumonia.

Cough *per se*, by virtue of the effort it requires, may increase the demand for oxygen and increase carbon dioxide. Appropriate treatment tending to diminish cough is often efficacious. One naturally has in mind fresh air, voluntary inhibition or control, counterirritation, medicated inhalations, sedatives, expectorants, etc., and local treatment of the pharynx and tonsils.

Dyspnea may result from pulmonary hemorrhage; sometimes by actual reduction of oxygen-conveying corpuscles, often by obstruction of the air passages and by the fright and cough which accompany the bleeding. In such cases opiates stand first as a therapeutic measure while accessory measures such as mustard or heat to the feet and an ice-bag to the chest may bring additional benefit.

**PNEUMOTHORAX.** Localized pneumothorax is usually small, often unrecognized, except upon radiosopic examination, and from the standpoint of dyspnea, unimportant.

Total pneumothorax, on the other hand, especially if sudden in onset, produces marked dyspnea and often shock.

Dyspnea results not so much from the fact that one lung has ceased to functionate but as a result of displacement of the mediastinal viscera and interference with the expansion of the sound lung. In open pneumothorax nothing relieves dyspnea so well as closure of the wound, if this can be accomplished. In open pneumothorax due to pulmonary disease this often happens spontaneously as a result of pulmonary collapse or bronchial occlusion.

Experimental evidence indicates that the dyspnea in open pneumothorax is due not to the short-circuiting of a large quantity of blood through the collapsed lung but to imperfect alveolar ventilation of the sound lung by the mediastinal movements. The mediastinum moves toward the sound lung during inspiration and away from it during expiration, thus lessening the pulmonary ventilation (Hewlett). With the patient at rest all the factors of respiration, gaseous exchange, carbon-dioxide tension and the mechanical factors are normal in persons with a collapsed lung. Ventilation is normal despite the greatly reduced vital capacity as long as there is no demand, such as that entailed by exercise, for increased ventilation. Even the response to carbon dioxide is normal up to the point at which respiration is trebled.<sup>18</sup>

Aside from opiates and psychic control but little can be accomplished in relieving dyspnea in pneumothorax. If distress continues aspiration of air or fluid from the pleura may be tried as a palliative measure until the physiological readjustment has been established.

**PLEURAL EFFUSION.** Dyspnea, especially upon exertion, is often encountered. It is usually proportional to the size of the effusion and the degree of cardiac embarrassment.

Reserve air, complementary air and residual air are decreased, the first two factors named resulting from a low vital and total capacity. The midcapacity, although actually decreased, is normal in its percentage relation to total capacity (Peabody). The dead space increases as the lung becomes encroached upon.

Inasmuch as this type of dyspnea is grossly mechanical in origin, removal of fluid from the pleura is the obvious treatment to be employed. Transudates in the pleural cavity are closely associated with insufficiency of the right heart, and hence cardiac medication is often of primary importance.

**PULMONARY EDEMA.** The causes of this condition are various and sometimes multiple and the diseases in which it may occur are numerous. Its treatment will therefore in large measure depend upon the etiological factor. However, taking pulmonary edema simply as a symptom, the dyspnea of which calls for treatment, there are certain measures which are sufficiently rational and effective to justify employment in the average case.

<sup>18</sup> Means, J. H., and Balboni, G. M.: Jour. Exper. Med., 1916, 24, 671.

Atropin sometimes alone, but more frequently combined with morphin, is often effectual, as is also digitalis. Dramatic improvement often follows phlebotomy, especially if venous pressure is high and the arterial pulse strong. If the edema be toxic in origin, as, for example, after phosgene inhalation, saline infusion should follow phlebotomy, for in these cases the blood becomes concentrated and the tissues oxygen-starved as a result of decreased volume. Whether a similar state of affairs exists in the spontaneous edemas of civil practice is, however, still a question for further study. One frequently encounters diminished respiratory function due to inadequate hemoglobin or erythrocytes in the blood, and it seems not at all unlikely that such a condition may be brought about by diminution in blood volume. In such event oral, rectal or intravenous saline therapy would be indicated. Until such treatment becomes effective, oxygen inhalations will tend to temporarily avert tissue asphyxiation. If the edema be obstructive in nature, and resulting from increased pressure in the pulmonary circulation, oxygen inhalation should follow bleeding.<sup>19</sup>

## FURTHER OBSERVATIONS ON THE NATURE AND TREATMENT OF CHRONIC NEPHROSIS.

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IN 1917 I published two papers,<sup>1 2</sup> in which I proposed to separate from the chronic nephritides certain forms of chronic parenchymatous nephritis which have shown themselves, by certain clinical features and by investigations of the constituents of the blood, to be of a distinct variety resembling the so-called chronic nephroses. I also proposed at that time a rational method of treatment for such cases, directed particularly toward restoration of normal conditions in the blood. The new viewpoints which I thus advanced have aroused considerable discussion both here and abroad.

In a clinical lecture on "Renal Dropsy," delivered at the Addenbrooke Hospital in August, 1918, Sir Clifford Allbutt<sup>3</sup> speaks of the striking results obtained by my method of treatment in a case of chronic parenchymatous nephritis. Box<sup>4</sup> in an address before the Lambeth Division of the British Medical Association quotes a similar case and speaks highly of the beneficial results of "Epstein's

<sup>19</sup> Matsnoka, Y.: *Jour. Path. and Bact.*, 1915, 20, 53.

<sup>1</sup> Epstein, Albert A.: *AM. JOUR. MED. SCI.*, 1917, 154, 638.

<sup>2</sup> Idem: *Jour. Am. Med. Assn.*, August 11, 1917, p. 444.

<sup>3</sup> *British Med. Jour.*, October 12, 1918, p. 395.

<sup>4</sup> *Ibid.*, March 13, 1920, p. 356.

High Protein Diet." McCay<sup>5</sup> refers to a case of nephritis, with generalized edema, which was cured by the adoption of the "high protein diet." Symes<sup>6</sup> says, "We have found this diet to be most efficacious in reducing nephritic edema, and further than this, it has resulted in a marked improvement in the patient's general condition and in reducing the amount of albumin in the urine."

McLean and De Wesselow<sup>7</sup> discuss my method of dietetic treatment, which they have adopted for the treatment of their "hydremic cases," namely, those marked with edema and anasarca. They agree "that a high protein diet often results in removal of the dropsy in chronic nephritis is certain," but they differ from me in the explanation of the cause of the removal. I shall discuss this question later. Wordley,<sup>8</sup> without stating the source of his information, says "It is generally accepted that a rich protein diet is of value in the treatment of certain chronic cases with persistent edema, on the ground that the plasma protein, being low, will be increased thereby." His own position relative to this is somewhat inconsistent; he accepts the principle and rejects it at one and the same time. Although in his conclusions concerning the cause of the diuresis which follows the high protein diet in such cases, he inclines to the view of McLean and De Wesselow, yet by his own protocol (Case X) he furnishes a good illustration in my favor and proves by actual analysis that which he attempts to disprove by argument. I shall also discuss this later.

On the other hand, Kahn<sup>9</sup> in a series of 37 cases does not seem to be able to find any which correspond to the group described by me. In none could he discover a change in the protein composition or the lipid content of the blood serum. He concludes his paper with the unwarranted statement that "The feeding of patients suffering with chronic parenchymatous nephritis on a protein-rich, fat-poor diet is rather a risky undertaking." No reasons are given. He ignores the fact that my treatment was designated for special cases with changes in the blood and urine of a specific type, the existence of which Kahn denies. It is therefore difficult to understand how he reached the above conclusion without the necessary experience.

In an editorial the *Journal of the American Medical Association*<sup>10</sup> discusses my views as well as the apparent inability of Kahn to find similar cases. It takes issue with his statement quoted above and concludes the discussion with the suggestion that "Clinical investigators should not abandon suggestions emanating from the

<sup>5</sup> Indian Med. Gaz., Calcutta, August, 1919, p. 54.

<sup>6</sup> British Med. Jour., April 10, 1920.

<sup>7</sup> Quart. Jour. Med., July, 1919, 12.

<sup>8</sup> Ibid., 1920, 14.

<sup>9</sup> Arch. Int. Med., 1920, 25, 112.

<sup>10</sup> Jour. Am. Med. Assn., 1920, 74, 19.

physiological laboratory without more conclusive assurances that they cannot apply to human disease."

Christian<sup>11</sup> in a paper in 1920, also in a chapter on subacute nephritis in *Oxford Medicine*,<sup>12</sup> where he quotes my dietetic treatment in detail, insists that he has not seen any beneficial results from it. His view coincides with that of Kahn as to the rarity of the group in which I have obtained such good results.

Geyelin too agrees with Kahn.<sup>13</sup> I will quote him in full in order to show the grounds upon which his views are based. He says: "My own experience during the past three years with cases of the type described by Epstein is in accord with that of Kahn. Bauman working in the wards of the Presbyterian Hospital has studied two patients who corresponded clinically to the Epstein type, and they both showed a high cholesterol content of the blood and a globulin to albumin ratio similar to those found in Epstein's cases. One case, a child, aged five years, had considerable edema, and an attempt to relieve this by high protein feeding resulted in gastrointestinal disturbance and had to be abandoned. On a low salt diet this patient improved slightly.\* In the second case the edema had largely disappeared on admission to the hospital, and continued salt restriction alone soon caused the remaining edema to disappear. Eight other cases clinically similar to those described by Epstein have been observed where salt and fluid restriction caused the edema to disappear. Unfortunately no blood protein or blood cholesterol determinations were made." He does not mention the total number of renal cases which he studied in the three years of which he speaks, yet he found 10 cases evidently belonging to my group. In only 2 cases was the blood examined by Bauman, and in both the results agree with mine. "Unfortunately" the remaining 8 cases were not examined as thoroughly as the others. In only 1 case out of the 10, therefore (that of a child), was a high protein diet instituted, and because of an upset stomach,† was discontinued.

This statement is very strange and incomprehensible, particularly when we compare it with the one made by Geyelin in another article published in a preceding number of the same journal.<sup>14</sup> "It is well recognized that protein restriction in certain forms of renal disease where there is no nitrogen retention, and when the blood-pressure is not high, is often carried to unnecessary extremes. No apparent effect is to be expected from protein restrictions under such conditions as mentioned, and in these cases a protein intake of 70 to 90 gm. per day is usually well tolerated, and is all the

<sup>11</sup> Jour. Am. Med. Assn., June 21, 1920, 74, 615.

<sup>12</sup> Christian, H.: *Oxford Med.*, vol. 3, Chapter X.

<sup>13</sup> *Prog. Med.*, December, 1920.

\* It would be of interest to know the subsequent history of this case.

† Not an unusual occurrence in renal conditions.

<sup>14</sup> *Prog. Med.*, 1919.



more permissible when the patient is under supervision and conditions are such as to permit of periodic estimations of the non-protein nitrogen in the blood. In certain types of nephritis (Epstein) overfeeding of protein would seem to be indicated." It would be illuminating, on the basis of his own statements, to know just wherein Geyelin's experience agrees with that of Kahn.

In the above quotations we find, so far as I am aware, the existing expression of opinions, *pro* and *con*, concerning my views. The predominating opinion (though foreign) is favorable, and the objections raised by my colleagues in this country lack substantiation. The question of the nature and treatment of chronic nephrosis resolves itself into at least five distinct propositions, and disagreement with one or another of these does not affect the problem as a whole.

The propositions are: (1) That chronic nephrosis is a clinical and pathological entity; (2) that chronic nephrosis is essentially a metabolic disease; (3) that chronic nephrosis is characterized by definite changes in the protein and lipid content of the blood serum; (4) that the water retention and consequent edema in this disease is of extrarenal origin and is due to reduced amount of colloid, and, hence, a lowered osmotic pressure of the blood; (5) that the feeding of large amounts of protein in the diet is the rational therapy for this disease. It may be added that cases of chronic glomerulonephritis with an intense and protracted albuminuria may at times show changes in the blood similar to those found in chronic nephrosis. In such cases the above findings constitute a late phenomenon, and the feeding of large amounts of protein in such cases may also be of benefit.

In the four years since the publication of my original papers (*loc. cit.*) I have had sufficient opportunity to test the soundness of my views. It seems to me, therefore, that it would be worth while to restate the matter in the light of further experience.

In order to clarify the type of case under consideration, and to which the high protein diet is to be applied, a few words concerning the subject of parenchymatous nephritis may not be out of place. Parenchymatous nephritis is the older term for certain groups of renal disease; it includes both the tubular and glomerular nephritis. The introduction of blood-pressure measurement in the clinic and of newer methods of blood chemistry in the laboratory have made it evident that this designation is unsatisfactory, for among the cases of parenchymatous nephritis there are at least two types which can be distinguished: (1) Those in which the glomeruli chiefly are diseased with secondary involvement of the tubules or interstitial tissue, or both, and which really represent an inflammation of the glomeruli—a glomerulonephritis; and (2) those cases in which tubular degeneration predominates or in which the glomeruli are not diseased. It was this consideration which

led Friedrich Müller to propose the term nephrosis for this second group of cases. Although the term nephrosis is not a happy one it has gradually been adopted by most writers in this field. In the newer monographs on renal disease, such as that of Volhard and Fahr,<sup>15</sup> Volhard,<sup>16</sup> Munk,<sup>17</sup> Richter,<sup>18</sup> etc., this term finds a definite place. This is rightly so, as it serves to separate (for the present at least) a group of cases which comply with special conditions. The newer studies on the blood chemistry and effusion fluids add support to the probable entity of this type of renal disease.

From the pathological standpoint, according to these authorities, chronic nephrosis is quite distinct. That the lesion in the kidneys in this condition is of an advanced degenerative type has been recently proved at autopsy.<sup>19</sup> From the similarity of the lesions to that produced by certain toxins and mineral poisons it is surmised that the disease (nephrosis) is due to an intoxication. Thus, for example, an acute tubular degeneration amounting in severe instances to tubular destruction is produced in poisoning of bichloride of mercury, bismuth, uranium, etc. Milder forms of parenchymal degeneration frequently occur in many febrile diseases, especially diphtheria, yellow fever and other infections. When the destruction of the tubular epithelium is not sufficient to produce death complete recovery takes place within a few weeks, as the tubules possess a remarkable capacity for regeneration. Although the kidney lesions in the acute and chronic forms of tubular nephritis (as just stated) may be alike, *it is questionable whether the cases which are encountered clinically, and which are termed "chronic nephrosis," ever actually result from an acute condition of the character described above.*

The true pathogenesis of this disorder must be left to the future to be determined. But many facts which we now possess strongly suggest that the disease begins as a metabolic disorder which leads primarily to the albuminuria (a diabetes albuminuricus), and secondarily to give rise to changes in the kidneys and to the other pathological and clinical sequelæ.

Chronic nephrosis is not a rare medical curiosity. Its frequency must be considerable, as allusions to the condition, by whatever term it may be designated, are numerous in the literature. Careful coördination of clinical data with chemical analysis of the blood and urine, however, is necessary for its recognition. Whether all cases of known etiology such as syphilis, tuberculosis and other general and focal infections and those of unknown causation are of the same order or not, the fact remains that cases of the type

<sup>15</sup> Die Brightsche Nierenkrankheit, Berlin, 1914.

<sup>16</sup> Die Doppelseitigen Haematogenen Nierenkrankungen, Berlin, 1918.

<sup>17</sup> Pathologie und Klinik der Nephrosen, Nephritiden und Schrumpfnieren, Berlin u. Wien, 1918.

<sup>18</sup> In Kraus's and Brugsch's System.

<sup>19</sup> Fahr: Loc. cit.

described by me exist and are fairly numerous. Munk<sup>20</sup> in speaking of "lipoid nephrosis," a type closely resembling mine, insists that the recognition of the entity of this condition is indispensable for a thorough clinical conception and the proper therapeutic management of this type of renal disease.

It is fair to admit that absolute standards for the differentiation of chronic nephrosis from the other types of "chronic parenchymatous nephritis" are still lacking, and it may at times be impossible to definitely place a given case until the therapeutic test (*i. e.*, a high protein diet) has been successfully applied. However, from our present knowledge the distinguishing features of chronic nephrosis are the following: The disease occurs in relatively young individuals. It is of obscure or unknown origin and bears no definite relation to known infectious diseases. In some instances pregnancy may stand in etiological relationship to the condition. Objectively it is characterized by a pronounced albuminuria with or without casts. The urine is usually free from blood elements. The blood-pressure is not elevated. At first the condition may be devoid of other gross manifestations; subjective symptoms may also be lacking and the exact time of onset frequently cannot be determined. Its development may be slow and insidious, but as it progresses oliguria and edema invariably develop. Pallor is usually very pronounced (the skin is of a dirty gray or putty-like color), and together with puffiness of the eyelids or swelling of the ankles may be the first symptoms to attract the patient's attention. Loss of appetite and a feeling of fatigue may be among the earlier symptoms. Headache, vomiting and diarrhea may also be present. Pain in the back may be encountered as a symptom, but not very frequently.

As stated above, with the progress of the disease the edema becomes marked. It reaches its highest degree in this disease and forms the chief clinical manifestation. Of great importance, also, is the state of the cardiovascular system. The heart is not enlarged, the blood-pressure is normal and in uncomplicated cases is never increased.

The urinary picture is characteristic. The quantity is much reduced, of a high specific gravity and contains large quantities of albumin.\* In my previous papers (*loc. cit.*) I stated that the daily output for weeks and months may amount to as much as 50 gm. a day. In the earlier stages the output of urinary excretory substances may be normal, but functional tests show renal deficiency, such as retention of chlorides, of nitrogen and diminished phenolsulphonephthalein excretion. Water retention may also occur in the early prædematous stages of the disease. The body -

<sup>20</sup> *Loc. cit.*

\* According to Munk, lipoid substances are present in the urine and can be readily detected microscopically.

tissues (other than subcutaneous) are evidently capable of storing up considerable fluid before showing definitely the presence of edema.<sup>21</sup> In fully developed cases the retention of chlorides and of nitrogen (as measured by test diets) may be quite marked, and yet the blood may fail to give evidence of such retention. This is particularly true in the edematous stages of the disease. The condition is not at all paradoxical. An explanation for it can be found in the greater distribution of the retained substances throughout the body in the water-logged tissues. In my earlier publications,<sup>22 23 24</sup> I have drawn attention to the fact that the non-protein constituents of effusion fluids approximate those of the blood in the same cases, both in point of quality and quantity. Denis and Minot<sup>25</sup> have also recently found that the non-protein constituents of the fluids (which belong to the class of crystalloids and among which are urea, uric acid and creatinin) occur in the same concentration in exudates and transudates as in the blood. They have also found that the concentration of the non-protein substances in ascitic fluid, for example, is easily influenced by diet. That the absence of increased concentration of the non-protein nitrogenous substances in the blood in cases of nephrosis is probably due to increased distribution of these substances throughout the body (or dilution) is further evidenced by the fact that both in the early prædematous as well as the postedematous stage (following treatment and general improvement) increased concentration of nitrogenous waste products as well as chlorides occurs. It may be added here, for the reasons stated, that estimations of soluble substances in the blood, in all cases associated with massive effusions or edema, do not accurately measure the quantity of such substances which are retained in the body. This is of importance in the interpretation of functional tests of the kidney.

Apart from the characteristics mentioned and from the clinical manifestations there occur in the blood certain changes which seem to distinguish this group from every other form of renal disease. These changes may be placed under two headings, primary and secondary.

As a primary change I consider the increase in the lipid content of the blood. Of the lipid substances it is cholesterol which has been especially studied. I called attention to this in my previous publications. Normally, cholesterol occurs in the blood as free cholesterol and as an ester, together varying from about 0.175 per cent to 0.225 per cent. Slight variations may occur in other forms of renal disease. But in the cases under consideration

<sup>21</sup> Epstein, Albert A.: *Medical Clinics of North America*, July 1920, 4, 145.

<sup>22</sup> Idem: *Loc. cit.*

<sup>23</sup> " *Loc. cit.*

<sup>24</sup> " *Jour. Exp. Med.*, 1912, 16, 719; 1913, 17, 444; 1914, 20, 334.

<sup>25</sup> *Arch. Int. Med.*, 1917, 20, 879.

the most marked increase has been noted. In my former publications I gave figures ranging from 0.333 per cent to 1.23 per cent. In other renal conditions, including surgical diseases, no such increase occurs. Occasionally a moderate rise may be encountered, but as a rule, this is associated with some other superimposed condition. Of interest, also, is the fact that in uremic cases, in those particularly showing a high nitrogen retention in the blood (the dry or so-called azotemic cases), the lipoid content is very much diminished. The cholesterol in such cases may fall as low as 0.06 gm. per 100 cc of blood. This is in conformity with the observations of Chauffard, Laroche and Grigaut.<sup>26</sup>

A milky appearance of the serum of certain nephritics was observed also by the older writers, notably by Bright<sup>27</sup> and also by Rayer.<sup>28</sup> However, careful chemical analysis of the blood in such cases has been made only in relatively recent times. In 23 cases of severe nephritis which Bloor<sup>29</sup> examined, the blood cholesterol values were practically normal. None of his cases were clinically of the type under discussion. In only one instance (Case XV, E 223) was edema present, and that was one of acute nephritis. Denis<sup>30</sup> found an increased cholesterol content in the blood in only 1 of 50 cases (Case C 253). This case is the only one in her series which might be called a "chronic parenchymatous nephritis." The first blood examination in this case yielded 0.475 per cent cholesterol and a second examination after a short interval showed 0.606 per cent cholesterol. Müller<sup>31</sup> found 0.84 per cent cholesterol in the blood in a case of nephritic lipemia. In a series of cases observed by Widal, Weill and Laudat<sup>32</sup> moderate increases in the blood cholesterol were found in a number of instances, but the highest value, 1.08 per cent, was obtained in a case associated with a very intense albuminuria. Beumer<sup>33</sup> found an increase in the cholesterol of the blood serum of nephrotic patients but not in other nephritides. Stepp<sup>34</sup> studied the cholesterol content of the blood in different forms of Bright's disease and found that in all cases of severe injury to the kidney parenchyma an increase in the cholesterol content of the blood occurred. On the other hand, types of nephritis in which interstitial change predominated did not show such increase. My own further observations only confirm the earlier ones. The cholesterol of the

<sup>26</sup> *Compt. rend. Soc. de biol.*, 1911, 70, 108.

<sup>27</sup> See reference. <sup>32</sup>

<sup>28</sup> See reference. <sup>32</sup>

<sup>29</sup> *Jour. Biol. Chem.*, 1917, 31, 575.

<sup>30</sup> *Ibid.*, 1917, 29, 93.

<sup>31</sup> *Physiol. Chem.*, 1913, 86, 469.

<sup>32</sup> *Semaine méd.*, 1912, 32, 529.

<sup>33</sup> *Monatschr. f. Kinderh.*, 1920, 18; abstract, *Jour. Am. Med. Assn.*, 75, 1300.

<sup>34</sup> *Deutsch. Arch. f. klin. Med.*, 1918, 127, 439-467.

blood has varied in the later series of cases from 0.3 per cent to 1.3 per cent.\*

The increase in the lipid content of the blood of chronic nephrosis constitutes a fundamental change and is of primary importance. It is undoubtedly of greater significance than is the lipidemia of diabetes. In the latter disease it occurs occasionally as a result of an excessive absorption and a perverted utilization of fat, and is frequently associated with an acidosis. Although the origin of the lipidemia in nephrosis is still obscure it is unquestionably of a different order from that which occurs in diabetes mellitus. If the lipidemia of chronic nephrosis were due to the accumulation resulting from ingested fat, restriction of fat should cause a fall in the lipid content of the blood; but that is not the case. The mere elimination of fat from the diet does not influence the lipidemia of chronic nephrosis to any great extent. We must therefore ascribe this lipidemia to other sources—in part, perhaps, to the mobilization of body fat, particularly as such cases show extreme emaciation when recuperation occurs. Tissue degeneration may also contribute its quota of lipid material to the blood (Koch and Voegtlin).

Like the albuminuria the lipidemia is a constant accompaniment of chronic nephrosis, and, in a measure, serves as an index of the degree of the severity of the disturbance. The inability of some investigators to find it can be accounted for only by the absence of appropriate cases (Bloor and Denis), or by the fact that their observations were based, in all probability, on cases of diffuse glomerular nephritis in which the lipid content is not necessarily increased (Kahn).

No reasonable explanation of the lipidemia can be found unless we assume that chronic nephrosis represents a specific type of disordered metabolism. That this deduction is warranted seems supported by the fact that in certain instances a hypothyroid state is definitely demonstrable. Basal metabolism has been found to be decreased where such studies have been made.<sup>35</sup> These studies have convinced me that we have a series of borderline cases on one side of which there are cases with a clinical picture of nephrosis and on the other side cases with distinct hypothyroidism and "frustes" forms of myxedema.†

As a secondary change I consider the reduction of the protein in the blood serum and the change in the ratio of albumin to globulin. Of these the change in the ratio of albumin to globulin is

\* By far the largest number of blood analyses for cholesterol have been made by my colleague, Dr. Joseph Reiss. Other members in the staff of the physiological department have contributed to this work. To all of them, and particularly to Dr. Joseph Reiss, I wish to extend my thanks for unselfish coöperation.

<sup>35</sup> Aub, J. C., and Du Bois, E. F., and Soderstrom, G. F.: Arch. Int. Med., May, 1917, p. 865.

† This will form the subject of a future report by the author and Lande.

possibly of greater importance than the reduction of total protein. In many cases it is the earliest manifestation. In my previous publications I gave figures for the normal and the changes occurring in the cases of nephrosis. Normally the protein of the blood serum forms about 6 to 8 per cent while the ratio of albumin to globulin is about 4 to 2 or 5 to 3, *i. e.*, the globulin forming about 37 per cent of the total protein. In nephrosis in my previously reported cases I found the figures for the total protein of the blood serum to average 3.928 per cent and the ratio of albumin to globulin to average 0.466 per cent of albumin to 3.426 per cent of globulin, the globulin forming 89.2 per cent of the total protein. Since then investigation has corroborated the above figures.

The reduction in the protein content of the blood serum is of twofold importance: (1) It stands in causal relationship to the edema, and (2) it furnishes an intimation to the effect of the albuminuria on the nutrition of the body, thus pointing a way to a rational therapeutic measure.\*

To summarize: We have then in the case of nephrosis a clinical picture characterized by a gradual onset, a protracted course, edema, anasarca and effusion of the serous cavities; by oliguria, marked albuminuria and occasional cylindruria, a high specific gravity which indicates ability to concentrate the urine. It is also characterized by the absence of any increased blood-pressure and any cardiac hypertrophy and by the absence of any marked nitrogen-retention in the blood. It is also characterized fundamentally by a marked increase in the cholesterol content of the blood, by a reduction in the total protein of the blood serum and by the inversion of the normal ratio of albumin to globulin. The whole presents a metabolic disturbance of nutrition. It is more pronounced in younger individuals. It stands in all probability in some relationship to states of hypothyroidism.

The above characteristics typify the pure forms of chronic nephrosis. Unfortunately renal diseases do not often pursue a clear-cut course. Undoubtedly there occur cases of glomerulonephritis to which the pathological picture of nephrosis is added, and *vice versa*. I have cited a case of the latter type in my article in the *Medical Clinics of North America*.<sup>36</sup> In practice they are common. The separation of the individual elements may at times be difficult. However, increase in the blood-pressure, a marked nitrogen retention and the presence of any blood in the urine

\* The use of the refractometer for the determination of the total protein or the globulins in the blood serum of cases of chronic nephrosis is inadvisable. The marked lipid content which is found in such sera interferes with the accurate reading for the protein. In fact the lipoids may interfere even with other methods of analysis, such as the precipitation of the globulins by means of ammonium sulphate. Where a marked lipoidemia is present it is necessary, therefore, to treat the serum first with ether, removing the ether by ventilation, precipitation of the globulins occurs, then, without any interference from the lipoids.

<sup>36</sup> Epstein, Albert A.: *Loc. cit.*

point to the glomerulonephritic element. Increase in the cholesterol, reduction in the protein and change in the albumin-globulin ratio in the serum point to the nephrotic element. It is of importance from the therapeutic standpoint to separate these elements, for with the abeyance of the glomerular inflammation treatment should be directed along the same lines as those indicated in cases of nephrosis. This will be discussed later. Numerous reasons exist for the belief that chronic nephrosis, or a renal disturbance closely resembling it, is a metabolic disorder from the beginning to the end. Nevertheless it is possible that certain of the phenomena which seem to characterize chronic nephrosis may occur in other types of renal disease and may be secondary to inflammation of the kidney. I refer particularly to cases of true nephritis which are accompanied by protracted albuminuria of a severe grade. Whether the albuminuria is the result of a general metabolic disturbance or the product of an inflammatory process in the kidney is quite immaterial as regards its ultimate effect on the blood. The relation between the albuminuria and the protein composition of the blood serum is a direct quantitative one. The more intense the albuminuria the greater will be the loss of serum protein (unless that loss is replaced somehow) and the more profound will be the effect on the general nutrition of the body. Whether the severe loss of protein substance can produce a lipoidemia also is a question which our present knowledge does not answer.

The fundamental point in the therapy of such cases is the loss of proteins in the urine and the consequent impoverishment of the blood in these substances.

The question has been raised by some observers as to the efficacy of the high protein diet in the treatment of the disease under discussion. Before advancing a rational therapeutic measure which should aim at the improvement of the fundamental chemical changes it is necessary, of course, for us to investigate how far these changes are responsible for the symptoms which objectively present themselves. Of these the most important one is the edema.

Since the time of Bright explanations for the cause of renal edema have been manifold. The modern theories may be classified under three headings: (1) Edema is the result of the inability on the part of the kidneys to excrete certain substances, such as water (Koranyi) and salt (Widal, Strauss, etc.). (2) Edema is the result of some injury to the capillary and endothelial walls: (a) As a result of an inflammatory condition (Cohnheim, Senator); (b) as a result of abnormal toxins due to destruction of the kidney cells, nephrolysin (Ascoli). (3) Edema is the result of some change in the tissues: (a) A colloid chemical change (Fischer); (b) a diminution of the elasticity of the subcutaneous tissues (Landerer).



It would lead us too far to attempt to examine in detail the basis for all these various theories. Just a cursory review is necessary to show their inadequacy:

1. The theory that edema is the result of the inability of the kidneys to excrete certain substances is at first glance very attractive when we notice the diminution of urine with the appearance of the edema. Koranyi and his pupils attempted to explain renal edema on the basis of the inability of the kidney to excrete water and the consequent water retention eventually resulting in the accumulation of fluid in the tissue spaces. That this explanation is not adequate is at once seen when we consider the cases of chronic glomerulonephritis with kidney insufficiency. We find here, according to some authorities, a marked hydremia, and yet these cases run, as a rule, until the end without any edema while cases of nephrosis with marked edema do not show any real hydremia.

Widal,<sup>37</sup> Strauss<sup>38</sup> and others believe the cause of edema to be the inability of the kidney to excrete salt. The retention of salt necessitates the retention of water to hold it in physiological solution. Widal's explanation is based especially upon the experiment of Widal and Javal on a case of renal edema, where they promptly produced edema four times by feeding the patient salt and by having first caused the edema to disappear by withdrawing the salt.

There is no doubt whatsoever that withholding the salt will in many cases (more particularly cardiorenal types) reduce the edema, and even cause it to disappear, but that the retention of salt is the underlying cause of the edema cannot be accepted. In cases of complete suppression of urine salt is retained with the other substances of excretion; here the concentration of the salt in the blood may reach to above 1 per cent without the production of edema. In chronic interstitial forms of nephritis (in hypertensive forms) retention of salt occurs but no retention of water.

2. The theory that edema is the result of an increased permeability of the capillary endothelial cell has its origin with Cohnheim. He assumed an inflammatory condition of the capillaries of the skin which caused this increased permeability. He was followed by Senator,<sup>39</sup> who assumed that the edema is not a consequent but a parallel phenomenon of the nephritis and due to injury of the capillary wall by the same toxin that caused the nephritis. This theory of increased permeability of the capillary endothelial wall seems to have found more favor with many of the modern writers on kidney disease.

Volhard<sup>40</sup> as well as Richter<sup>41</sup> subscribe to this theory, although they do not accept the idea that the injury to the capillary wall is an inflammatory one.

<sup>37</sup> Bull. et mém. Soc. méd. d. hôp. de Paris, June 12, 1902.

<sup>38</sup> Die chronischen Nierenentzündungen, etc., Berlin, 1908.

<sup>39</sup> Lehrbuch der Nierenkrankheiten, Wien und Leipzig.

<sup>40</sup> Loc. cit.

<sup>41</sup> Loc. cit.

Against the theory of the inflammatory condition of the capillaries we have the fact that the edema of cases of nephrosis is not of an inflammatory character. In a previous paper<sup>42</sup> I have shown that the edema fluid in these cases is made up principally of salt and water and that it contains only a trifling amount of protein. Against the view of Senator is also the fact that glomerulonephritis occasionally runs its course without any edema. Moreover, recent observations in experimental nephritis show that capillary permeability is diminished and not increased.<sup>43</sup>

Ascoli<sup>44</sup> assumes that during the course of nephritis, toxic substances and "nephrolysins" are produced which injure the endothelial cells of the capillary. This has received support from the fact that some observers have found substances with a lymphagogue action in the serum of the blood and edema fluid in cases of nephritis (Kast, Sterling). No definite nephrolysins have, however, been isolated, and the assumption of Ascoli is purely hypothetical.

3. These theories are based on the assumption of some change in the tissues. Of these, Fischer's colloid chemical theory has aroused much notice. Fischer assumes an increased imbibition of the tissue colloids under the influence of an increased avidity of the cells. This theory is not acceptable for many reasons, a few of which stand out prominently. An increased avidity of the tissue cells for fluid would not account for the presence of fluid between the cells which constitutes edema. Also, it has been shown that the tissues in edema are not abnormally acid and that an increase in acidity sufficient to cause a marked imbibition of the tissue colloids would result in the death of the tissue.

Landerer<sup>45</sup> assumed the edema to be due to a diminished elasticity of the tissues, but Boenninger<sup>46</sup> points out the objections to this. In old people with loose skin the elasticity is undoubtedly reduced, and yet no edema results. The same is true of the lax tissues which persist in cases after resorption of the edema.

From the review of these theories it will be seen that although they are many and varied, yet they do not offer a reasonable explanation. It is necessary therefore before attempting to explain the causes of edema to discuss the principles underlying the formation of lymph and tissue fluid. We must distinguish between the various forms of fluid which together are often termed "lymph." First, there is the transudate which leaves the circulation through the capillary wall and which contains all of the nutrition material necessary for the cell. Then the tissue fluid which contains some of the transudate but mixed with it—some of the waste products

<sup>42</sup> Epstein, Albert A.: *Loc. cit.*

<sup>43</sup> Chisholm, Boycott and Douglas: *Jour. Path. and Bacteriol.*, 1914, 19, 265. Bogert, Underhill and Mendel: *Am. Jour. Physiol.*, 1916, 41, 189.

<sup>44</sup> *Vorlesungen über Urämie*, Jena, 1903.

<sup>45</sup> *Die Gewesspannung*, etc., Leipzig, 1884.

<sup>46</sup> *Ztschr. f. exp. Path. u. Therap.*, 1, S. a.

of cell metabolism. Finally, there is the fluid which is contained in the lymphatic vessel or lymph proper.

The tissue fluid serves as a middleman between the circulation and the tissue while the lymph serves the purpose of removing any excessive transudate as a result of increased cell activity. This is shown best in the case of glandular activity such as that of the salivary glands, and better still in the case of the liver. Increased liver activity at once increases the transudate, and as a consequence the lymph flows from that organ, and, following this, from the thoracic duct.

Normally a satisfactory balance is maintained between the amount of transudate, tissue fluid and lymph flow. It is maintained at a low level of activity in the case of the resting limbs and at a higher level of activity in the case of the glandular organs.

What are the forces, then, which maintain this balance? What causes a disturbance of this balance, and with what result?

In this field, as in that of the kidney, the dispute has been between those who believe in the active secretion of the endothelial cell of the capillary wall and those who believe in filtration through the capillary wall. Modern physiologists, as Starling,<sup>47</sup> assume the endothelial cell to act as a filtering membrane of variable permeability, and that the factors responsible for the transudations are of two classes: (1) Mechanical, depending upon pressure in the capillaries; (2) chemical, depending upon the constituents of the blood and tissue fluid and upon the processes of diffusion and osmosis. By the term variable permeability is meant the condition of the capillary wall in various parts of the body which vary in regard to completeness. This is again best illustrated in the case of the liver, where the capillary endothelial lining is discontinuous—that is, the capillaries lack a complete endothelial wall. The capillaries of the intestines are less permeable than those of the liver, but more so than those of the limbs. In the intestine and in the liver, therefore, an increase in the capillary pressure will at once cause an increase in the transudate and in the flow of lymph (Starling).<sup>48</sup>

Although both factors, the mechanical and the chemical, are concerned in every part of the body, the chemical factor comes into more play in the limbs where the capillary wall is less permeable than is the case in the liver or in the intestine. Their interchange between the blood and tissue fluid is dependent not only upon filtration but also upon the osmotic forces of the dissolved substances. Here the breaking-down of large molecules into smaller ones in the process of muscular activity increases the number of molecules with the consequent increase in osmotic pressure in the tissue fluid. This causes an increase in the transudate from the

<sup>47</sup> Principles of Human Physiol., Philadelphia, 1920.

<sup>48</sup> Loc. cit.

blood—that is, in the flow of fluid from the lower to the higher concentration. The opposite is true when the blood becomes more concentrated, such as after an injection of dextrose which results in the flow of fluid from the tissue to the blood.

We have therefore normally these forces of intracapillary pressure and of the osmotic force, of the dissolved substances, normally balancing each other to maintain a constant interchange between the blood and the tissues, and varying with the activity and the demand of the tissues.

Anything, therefore, which causes a change in the intracapillary pressure or in the osmotic pressure, concentration in the dissolved substances will at once cause a disturbance in the tissue fluid. A simple illustration of the result of changing the intracapillary pressure is the effect of hemorrhage. This is at once followed by a universal fall in the capillary pressure below that of the surrounding tissue fluid, and this results in the backward filtration which makes up for the loss of the fluid.

Increase in the intracapillary pressure must be equalized by a corresponding increase in the osmotic concentration of the blood, and if this does not occur is followed by an increase in the amount of the transudate; and if the increased amount of transudate is not promptly removed, accumulation of fluid in the interspaces will result (cardiac decompensation, hepatic cirrhosis and localized inflammatory processes).

If the intracapillary pressure is not effected but there is an increase in the osmotic pressure in the blood, there will be an increased absorption of fluids from the surrounding tissues into the blood stream with resulting dryness of the tissues. This is the case in diabetes with a high sugar content in the blood. Again, if the osmotic pressure of the blood sinks this will remove the counterbalance of the normal intracapillary filtering pressure, and the result will be an increased transudate and increased accumulation of fluid in the interspaces.

With these principles in mind we may attempt an explanation of edema.

The characteristic of renal edema fluid which distinguishes it from the fluid of cardiac, or static, or obstructive edema is the low protein content. This may be as low as 0.1 per cent, whereas in the case of cardiac edema the protein content of the fluid is much higher. This also distinguishes the nephrotic edema from the edema of glomerulonephritis, where the protein content of the edema fluid is also higher. Recently, Beckman<sup>49</sup> found the edema fluid in tubular disease of the kidney to contain protein generally under 0.1 per cent; the highest protein content he found in glomerulonephritis.

These types of edema—namely, cardiac, nephritic and nephrotic—can be distinguished, therefore, by their protein content. They are also produced differently.

Cardiac edema is the result of relative myocardial insufficiency. The diminution of the volume output of the heart causes a slowing of the venous blood flow, a stasis with enormously increased capillary pressure. The balance between the intracapillary pressure and the osmotic force of the blood is disturbed in favor of the intracapillary pressure, and the result is increased filtration, with an increase in the transudate, not varying a great deal in its constitution from that of the blood plasma. Cardiac edema occurs especially in the dependent portions of the body where the pressure is greatest.

The edema of glomerulonephritis is also probably due to increased capillary pressure with increased filtration. Here the edema is generalized because the increase in the capillary pressure is general and is due to the increase in the blood-pressure with narrowing of the capillaries all over the body. With the method elaborated for observing skin capillaries under the microscope by Weiss<sup>50</sup> and others, it has been found that in acute glomerulonephritis with increased blood-pressure the blood in the capillaries did not flow evenly, but that the flow was interrupted and the capillaries narrow and elongated (Volhard).

The edema of nephrosis is also due to a disturbance in the balance between the intracapillary pressure and the osmotic force of the blood. But the fault here is with the osmotic force. According to the investigations of Starling the proteins of the blood exert an osmotic pressure of 25 to 30 mm. of mercury. In my paper concerning the causation of edema in chronic parenchymatous nephritis<sup>51</sup> I advanced the theory that it is the loss of protein through the urine which causes the diminution of the osmotic force of the blood: That this leads to a disturbance in the balance between the osmotic force and the intracapillary pressure, and by virtue of this the osmotic power of the tissue fluid at the same time becomes relatively increased, resulting in the attraction of fluid from the blood to the tissue fluids. I stated, then, that the loss of protein from the blood serum is sometimes equivalent to from 60 to 70 per cent of the total. "In terms of osmosis this loss of protein represents a pressure equal to 20 to 24 mm. of mercury, a factor sufficient to disturb the equilibrium in the exchange of fluid between the blood and the tissues. . . . More precisely the deficit in the serum protein causes a fall in the osmotic pressure of the blood. This disturbance does not only favor the passage of fluid from the blood to the tissues but also gives to the tissues the controlling power to absorb and retain fluid."

<sup>50</sup> Deutsch. Arch. f. klin. Med., vol. 119, S. 1.

<sup>51</sup> Epstein, Albert A.: Loc. cit.

The above theory that edema is due to a loss of protein from the blood serum has received added support by the study of the so-called "war edema," and by experimental production of edema.

War edema began to appear in the Central European States in 1915. Those who studied it noticed the resemblance of the disease to what had been described in previous wars under different names. Bigland<sup>52</sup> observed edema in Turkish prisoners of war in Egypt. He noticed its resemblance to what had been called "epidemic dropsy" in India and to the edema observed in South Africa. Jansen<sup>53</sup> made extensive studies concerning the pathogenesis of this disease. His studies are of extreme interest, for they show conclusively that the edema is the result of loss of protein to the body through insufficient nutrition. His cases showed a distinct diminution of the protein in the blood serum. I quote from Table VIII, page 171:

There were found:

In 10 investigations . . . .	8.5 to 6.5 protein, normal.
In 10 investigations . . . .	6.4 to 6.0 protein, subnormal.
In 16 investigations . . . .	5.9 to 5.0 protein, much diminished.
In 4 investigations . . . .	4.7 to 4.0 protein, very much diminished.

Falta<sup>54</sup> also ascribes the war edema to insufficient protein in the food. The experimental studies of edema by Denton and Kohman<sup>55</sup> and by Kohman<sup>56</sup> have shown the importance of protein in the production of edema. They caused the appearance of edema in animals under protein undernutrition. On feeding carrots only to young rats a number of the animals developed edema. When part of the diet was replaced by protein, such as casein, the edema did not appear.

From the above it can be seen that the theory of edema advocated by me does not only seem plausible, but is gradually becoming solidly established. Still more support is supplied by the effect obtainable from a proper therapy in cases of chronic nephrosis (Albutt, Box, Syms, McLay, McLean and De Wesselow and Wordley).

Based on the above reasoning and conclusions I have proposed in my previous publications<sup>57</sup> a rational dietetic treatment. This consists in the feeding of a high-protein, fat-free, carbohydrate-poor diet. The protein is to replace the protein lost by way of the urine so as to increase the osmotic force of the blood. This, of course, does not occur by direct reentry of the ingested proteins

<sup>52</sup> *Lancet*, January 3, 1920, p. 243.

<sup>53</sup> *Deutsch. Arch. f. klin. Med.*, 1919-1920, 131, 144.

<sup>54</sup> *Wien. klin. Wchnschr.*, 1917, S. 1637.

<sup>55</sup> *Jour. Biol. Chem.*, 1918, 36, 249.

<sup>56</sup> *Proc. Soc. Exper. Biol. and Med.*, 1919, 16, 121; *Am. Jour. Physiol.*, 1920, 51, 185.

<sup>57</sup> Epstein, Albert A.: *Loc. cit.*

into the blood but by furnishing the necessary building blocks for the reconstruction of the protein lost from the body. The fat-free, carbohydrate-poor part of the diet is to compel the body to utilize the protein as well as the lipoids which are present in the blood stream. The diet has been very efficient in my hands, and in the hands of others also, as indicated from the results mentioned in the beginning of this paper.

It has been supposed that protein feeding increased the albuminuria of nephritis. In my previous publications<sup>58</sup> I have drawn attention to the fact that protein feeding has no such effect. Eichhorst<sup>59</sup> claims that the protein in the diet does not affect the albuminuria one way or another. More recently Wordley<sup>60</sup> made observations on this point and arrived at the same conclusions.

McLean and De Wesselow,<sup>61</sup> who had good results with the high protein diet, ascribed the removal of the edema not to the increase of the protein in the blood but rather to the increase in urea as a result of the breaking down of added protein. As evidence they cite the increase in the urea content of the blood and the well-known diuretic action of urea. In answer to this it may be said that the increase in the urea content of the blood may as well not be the cause of the disappearance of the edema but rather, and in all reason is, the result of the edema fluid being reabsorbed into the blood stream preparatory to its elimination by the kidney. As the edema fluid is reabsorbed in response to the osmotic force of the increased protein in the blood it carries with it the urea which it contains. As the urea in the blood and in the edema fluid are in osmotic equilibrium the urea in the blood cannot exert any osmotic pressure, to which McLean and DeWesselow partly ascribe the removal of edema.

I have referred to the work of Denis and Minot,<sup>62</sup> which shows the effect of feeding protein on the non-protein composition of ascitic fluid. Being evenly distributed in the blood stream and the tissue fluid the urea cannot be said to possess an osmotic pressure favoring the passage of fluid in one direction or another, so that the disappearance of the edema cannot be ascribed to that cause. As for the effect of the urea as a direct diuretic, definite evidence is lacking. The persistence of an elevated non-protein nitrogen content in the blood in some cases, long after subsidence of the edema, shows the lag on the part of the kidneys to eliminate the nitrogenous waste products as contrasted with the prompt elimination of water.

Wordley<sup>63</sup> holds to the same opinion about the cause of the removal of edema as do McLean and De Wesselow, yet in his

<sup>58</sup> Epstein, Albert A.: *Loc. cit.*

<sup>59</sup> Eichhorst: See references <sup>1</sup> and <sup>2</sup>.

<sup>60</sup> *Loc. cit.*

<sup>62</sup> *Loc. cit.*

<sup>61</sup> *Loc. cit.*

<sup>63</sup> *Loc. cit.*

Case X the evidence is strongly in my favor. I cite his figures in detail:

CASE X.			
No. of experiments.	Protein per cent.	Diet.	Remarks.
1 . . . . .	2.427	Fish	Feels fairly well; edema increasing.
2 . . . . .	2.328	Fish	Blood urea, 94 mg. per 100 cc; plasma protein, 5.06 per cent; multiple punctures of legs performed.
3 . . . . .	1.76	Milk	Draining freely from punctures.
4 . . . . .	1.456	Milk	Stopped draining.
5 . . . . .	1.988	Milk	Less edematous.
6 . . . . .	1.756	Milk	Plasma protein, 8.2 per cent; blood urea, 52 mg. per 100 cc; urinary chlorides, 0.23 per cent; is much better.
7 . . . . .	2.06	Fat and carbohydrate salt-free.	
8 . . . . .	1.84	Fat and carbohydrate salt-free	Slightly more edematous.
9 . . . . .	2.068	Fat and carbohydrate salt-free	Much more edematous; drain with Southey tubes; urinary chlorides, 0.076 per cent.
10 . . . . .	2.8	Fat and carbohydrate salt-free	Still draining; intensely edematous; much worse.
12 . . . . .	2.5	Fat and carbohydrate salt-free	Blood urea, 198 mg. per 100 cc; plasma protein, 4.57 per cent.
13 . . . . .	2.18	Fat and carbohydrate salt-free	Tremendous edema; moribund.

It will be seen from the above that with the improvement of the edema the plasma protein increases from 5.06 per cent as noticed in Experiment 2 to 8.2 per cent as noticed in Experiment 6. Again it will be noticed that the improvement occurred when the patient was on a fish diet, and that when put on a fat and carbohydrate diet; which was also salt-free, the edema increased to a marked degree, and at the same time the plasma protein sank to 4.5 per cent as noticed in Experiment 12. This case is a beautiful illustration of the relation of the plasma protein to the causation of edema.

The diet that I employ is the same one that I evolved in my previous publication.<sup>64</sup>

#### DIET EMPLOYED.

	Daily amount.
Food value . . . . .	1280 to 2500 calories
Proteins . . . . .	120 to 240 grams
Fats (unavoidable) . . . . .	20 to 40 "
Carbohydrate . . . . .	150 to 300 "

<sup>64</sup> Epstein, Albert, A.: Loc. cit.



*Articles of Food Used.* Lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea and cocoa.

The fluid allowed is restricted to the quantity present in the food, plus that which is necessary for the comfort of the individual patient, amounting usually to 1200 to 1500 cc. The amount of salt allowed is the quantity sufficient to make the food palatable.

I might state at this point that the use of pure proteins in the feeding of cases of chronic nephrosis is at present under investigation.

Disappearance of the edema and even marked diminution of the albuminuria does not mean a complete cure of the nephrosis. A complete cure is established when, besides the disappearance of symptoms, there is also a normal state of the blood as regards the cholesterol, protein and the albumin-globulin ratio.

In conformity with the view that chronic nephrosis is a metabolic disease related to a state of hypothyroidism, I have used thyroid gland therapy in a number of cases which were more obstinate, and I had gratifying results. The relationship of the thyroid gland to obscure cases of edema has been made the subject of a study by Eppinger.<sup>65</sup> In his work he presents most remarkable data of increased diuresis following administration of the thyroid gland in various forms of edema. No basal metabolism studies, however, are given. Volhard<sup>66</sup> has also seen good results from thyroid gland administration.

The effect of thyroid feeding upon some cases of nephrosis is so striking that there can be but little doubt as to the relation of thyroid deficiency to this disease. The frequent occurrence of nephrosis in children and the usual gravity of the condition in such cases suggest the possibility of its being due to a deficiency of some factor in the food—possibly a vitamine.

In this connection the experience of writers on war nephritis is of interest who found a peculiar tendency in the kidneys to fatty degenerative changes, and who ascribe these changes to disorders of nutrition (Munk).<sup>67</sup> This possibility should be borne in mind in future studies of the subject.

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## THE PREVALENCE OF FREE HYDROCHLORIC ACID IN CASES OF CARCINOMA OF THE STOMACH.

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ACHLORHYDRIA is so frequently associated with carcinoma of the stomach that one acquires the habit of looking for it as a diagnostic

<sup>65</sup> Zur Pathologie und Therapie des menschlichen Odems, Berlin, 1917.

<sup>66</sup> Loc. cit.

<sup>67</sup> Loc. cit.

sign of carcinoma. This habit grows until one hesitates to make a diagnosis of carcinoma of the stomach in the presence of any appreciable amount of free hydrochloric acid in the gastric secretions. Clinicians who have the opportunity to observe the results of fractional analysis of the gastric contents find that achlorhydria is not essential to the diagnosis of gastric carcinoma. As a means of corroborating this finding a statistical review was undertaken of the analysis of gastric contents in cases in which operation was performed for cancer at the Mayo Clinic during the years 1918, 1919, and 1920. Since the results for each year were quite uniform the data were studied as a whole. When the surgeon noted the location of the lesion in the pyloric, middle, or cardiac portion of the stomach this was considered in classifying the data.

During the three years, there were 551 patients with gastric carcinoma and 80 patients with carcinomatous ulcer operated on. Of the latter, with one exception, a case of gall-stone, gastric lesions were clinically suspected. Forty-five per cent of the cases were diagnosed ulcer, 41.25 per cent cancer, and in 12.15 per cent the diagnosis was suspected gastric malignancy.

The gastric acidity was first classified separately according to the location of the lesion and then together. Of the 551 patients with carcinoma, 47 did not have test meals because they were too weak to stand them, because the stomach was found empty on aspiration, because of a mistaken diagnosis, because the patient's condition demanded an emergency operation and so forth. In 122 patients the lesions were not located by the surgeon, although resection was performed. In 66 patients the condition was found inoperable. An exploration or a gastro-enterostomy only was made for the relief of an obstruction. In 297 patients the lesions were in the pyloric end of the stomach, in 27 in the middle portion, and in 39 in the cardiac end. These data were taken from patients who were operated on; this accounts for the preponderance of pyloric lesions which are favorable for surgical measures, whereas lesions higher up are not accepted by the surgeon (Table I).

TABLE I.—CARCINOMA.

	Cases.	Per cent.	Achlorhydria.	Per cent.	Hypocidity.	Per cent.	Normal.	Per cent.	Hypercidity.	Per cent.	No test meal.	Per cent.
Not located	122	22.14	67	54.9	12	9.83	22	18. +	4	3.27	17	13.9
Inoperable	66	11.97	40	60.6	8	12.12	11	16.66	4	6.06	3	4.54
Pyloric . .	297	53.9	154	51.85	53	17.84	54	18.18	15	5.05	21	7.07
Middle . .	27	4.9	11	40.74	11	40.74	5	18.51	0	...	0	
Cardiac . .	39	7.07	24	61.54	3	7.69	4	10.25	2	5.12	6	15.38
Ignoring location.	551	.....	296	53.72	87	15.78	96	17.42	25	4.53	47	8.53

The normal amount of free hydrochloric acid was estimated at from 20 to 40. The classification of the lesions according to location revealed little of importance. However, in 51.85 per cent of the pyloric lesions achlorhydria was present and the pyloric end of the stomach is not supposed to possess any acid-forming cells that could be destroyed by a new growth. In 5.05 per cent of the pyloric lesions the values were hyperacid. In the cardiac portion, the location of the acid-forming cells, the achlorhydria was 61.54 per cent and the hyperacid values 5.12 per cent.

The location of the lesion apparently does not materially influence the degree of the acidity. It is impossible from these statistics to determine the percentage of occurrence of any one degree of acidity in any one division of the stomach. Pyloric lesions predominate in patients operated on and therefore they have the highest percentage occurrence in any one degree of acidity.

Attention is called to the total findings in Table I, in which the gastric analyses have been studied without reference to the location of the lesion. Only 53.72 per cent., about one-half of the patients, had achlorhydria; 15.78 per cent had free hydrochloric acid in small amounts. In 17.42 per cent the gastric acidity was normal and 4.58 had hyperacid values. The sum of the last two figures show that 21.95 per cent, or more than 1 case out of 5, had normal or hyperacid values. Thirty-seven and seventy-eight hundredths per cent, or about 2 out of 5 cases, had a certain amount of free hydrochloric acid. The occasional marked difference between free and total acidity is shown in Table II; this occurs particularly in pyloric lesions. It cannot be explained by obstruction with retention of the neutralizing food, because in the cases in which the difference in the acidity was more than 40 there was obstruction only in 34.28 per cent.

In Table III are data concerning gastric ulcer undergoing malignant change. Only 22.5 per cent of cases had hypoacid values. The sum of the percentages of those having some acid (hypoacidity, normal acidity and hyperacidity) is 72.5. The extent of the malignancy therefore seems to influence the amount of free acid because the same total in carcinoma cases was only 37.78 per cent. In Table IV it may be seen that out of 631 cases of gastric carcinoma in all stages of development 49.76 per cent showed achlorhydria; 15.2 per cent hypoacidity, 19.96 per cent normal acidity and 6.97 per cent hyperacidity. The sum of the last two figures shows that 26.93 per cent, or about 1 case out of 4, had normal or hyperacid values. Forty-two and fourteen hundredths per cent had some free hydrochloric acid present. One should expect then to find free hydrochloric acid in about every other case.

It is seen, therefore, that achlorhydria is present in a little less than one-half of the cases of carcinoma of the stomach. Normal or hyperacid values can be expected in more than one-fourth. The



TABLE III.—CARCINOMATOUS ULCERS.

	Cases	Per cent.	Achlorhydria	Per cent	Hypocidity.	Per cent	Normal	Per cent.	Hyperacidity.	Per cent.	No test meal.	Per cent.
Not located	22	27 50	6	27 27	3	13 63	5	22 72	7	31 36	1	4 54
Inoperable	50	62 5	10	20 00	.	12 00	22	44 00	12	24 00	.	
Pyloric . .	3	3 75	1	33 33	.	.	2	66 66	.	.	.	
Middle . .	5	6 25	1	20 00	.	.	1	20 00	.	.	3	60 00
Cardia . .												
Ignoring location	80	.....	18	22 50	9	11 25	30	37 5	19	23 75	4	5 00

TABLE IV.—CARCINOMA AND CARCINOMATOUS ULCERS.

	Cases.	Per cent	Achlorhydria.	Per cent.	Hypocidity.	Per cent.	Normal.	Per cent.	Hyperacidity.	Per cent.	No test meal.	Per cent.
Not located	144	22 82	73	50 69	15	10 41	27	18 75	11	7 63	18	12 5
Inoperable	66	10 45	40	60 6	8	12 12	11	16 66	4	6 06	3	4 54
Pyloric . .	347	54 99	164	47 26	59	17 0	76	21 9	27	7 78	21	6 05
Middle . .	30	4 75	12	40 0	11	36 66	7	23 33	.	.	.	
Cardia . .	44	6 97	25	56 81	3	6 81	5	11 36	2	4 5	9	20 45
Ignoring location	631	.	314	49 76	96	15 21	126	19 96	44	6 97	51	8 08

acid values represent the highest reading obtained by a fractional analysis of the gastric contents; this, I believe, gives a greater chance of obtaining higher and more accurate values than the single tubing.

### THE RELATION OF ACROMEGALY TO THYROID DISEASE: WITH A STATISTICAL STUDY.\*

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THE view that acromegaly is caused by hyperactivity of the anterior pituitary body after epiphyseal union has taken place is

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generally accepted. Cushing,<sup>1</sup> however, adduced experimental evidence to show that the disease is due to some perversion of secretion rather than merely to an excess of normal secretion.

With the slow and gradual development of the affection the sella turcica dilates into a cavity of variable size, as shown by a roentgen-ray examination. In practically all cases of acromegaly that have come to autopsy enlargement or disease of the hypophysis has been found, with a corresponding dilatation of the sella turcica and persistence of the thymus in most instances. The new growths of the pituitary gland may be of different character, *e. g.*, adenoma, sarcoma, carcinoma and cystic degeneration. It is generally held that the majority are adenomata. Sternberg<sup>2</sup> states that the acute form of acromegaly is due to a rapidly progressive tumor, frequently sarcoma, of the hypophysis. The enlargement may be due to functional hypertrophy with or without hyperplasia of the chromophile cells.

On the other hand it has been shown that destructive lesions of this gland may be at times unaccompanied by clinical symptoms of acromegaly.<sup>3</sup> In 1891 one of us (Anders) and Henry W. Cattell reported to the Philadelphia Neurological Society a hemorrhagic tumor of the pituitary body and infundibulum which had been unattended with any signs of acromegaly during life.

Conversely, Arnold and Ponfick<sup>4</sup> have reported cases of acromegaly with the pituitary glands normal in all respects. It is true, as pointed out by Friedman,<sup>5</sup> that all ductless-gland disturbances may manifest themselves clinically without gross or microscopical changes. Hemmeter<sup>6</sup> has also emphasized the occurrence of endocrine syndromes without actual pathological alterations. These are termed "ductless-gland neuroses." Among predisposing factors in acromegaly, the role of some of which are still in doubt, are race, age, sex, heredity and trauma, to which detailed reference will be made hereafter.

In 1886 Rogowitsch,<sup>7</sup> and later Stieda<sup>8</sup> and Hofmeister,<sup>9</sup> noted hypertrophy of the pituitary after removal of the thyroid in rabbits. Bourneville and Bricon<sup>10</sup> state that in sporadic cretinism in which the thyroid is lost the pituitary has been found to be enlarged. Boyce and Beadles<sup>11</sup> and other observers found an increase in size

<sup>1</sup> The Pituitary Body and its Disorders, p. 10.

<sup>2</sup> Nothnagel's Handbook, 1897, p. 7.

<sup>3</sup> Jokeloff: Virchow's Archives, vol. 13.

<sup>4</sup> Quoted by Cushing: *Loc. cit.*, p. 20.

<sup>5</sup> New York Med. Jour., 1921, 113, 370.

<sup>6</sup> *Ibid.*, 1914, 99, 101.

<sup>7</sup> Modern Medicine (Osler and McCrae), 1915, 4, 803.

<sup>8</sup> Ueber das Verhalten der Hypophysis des Kanninchens nach Entfernung der Schilddrüse, Ziegler's Beiträge, vol. 10.

<sup>9</sup> Fortschr. d. Med., 1892, No. 4.

<sup>10</sup> Arch. d. Neurol., 1886.

<sup>11</sup> Bacteriol. and Pathol., 1892, 1, 223 and 359; February, 1893. Pathologic Reports, University College, London, 1892-93, vol. 1.

of the pituitary gland in hyperthyroidism, while Abram<sup>12</sup> noted changes in this gland in a case of carcinoma of the thyroid. Marie and Marinesco<sup>13</sup> described a case of acromegaly in which there was simple hypertrophy of the thyroid and thyroid-like tissue of the hypophysis. Schöneman<sup>14</sup> in 85 cases of goiter found marked changes in the pituitary in all but one instance.

Conversely, in animals subject to experimental hypophysectomy, definite histological alterations in the thyroid have been observed. For example, Caselli<sup>15</sup> found hypertrophy of the entire thyroid apparatus. The view of Comte<sup>16</sup> and Hoskins<sup>17</sup> that these two glands can function vicariously for one another is supported by the results of total or nearly total extirpation of the hypophysis and those of thyroidectomy.

Of 15 cases of pituitary disease in Cushing's series, in which the thyroid was examined microscopically, all showed "a low epithelium with excess of colloid." It should be noted that at the time of his examinations all of the cases were evidencing signs of glandular insufficiency.

Exner<sup>18</sup> relates that in 2 of Hochenegg's cases of acromegaly, after partial extirpation of the pituitary, enlargement of the thyroid occurred. Says Cushing,<sup>19</sup> "It is my impression that the gland is most liable to show enlargement in individuals with clinical evidences of past hyperpituitarism"—suggesting, in other words, that the same underlying biochemical factor causes a hyperplasia of both structures rather than that the thyroid assumes a compensatory and vicarious role for the hypophysis. Observations upon tumors of the hypophysis were described as early as 1810, when Wenzel<sup>20</sup> tried to link epilepsy with diseases of the pituitary. To Friedreich<sup>21</sup> we owe the first attempt to formulate the symptoms of pituitary new growths.

Cushing<sup>22</sup> has described cases of acromegaly in which with overgrowth and overactivity of the anterior lobe are associated symptoms of posterior lobe insufficiency, *i. e.*, adiposis, increased sugar tolerance, polyuria, polydipsia, subnormal temperature, dry skin, loss of hair, epileptiform disturbances and the like.

Pineles<sup>23</sup> has emphasized the clinical relationship between acro-

<sup>12</sup> Liverpool Med.-Chir. Jour., July, 1896.

<sup>13</sup> Anatomie pathologique de l'Acromegalie, Arch. d. méd. exp., 1891.

<sup>14</sup> Virchow's Archives, 1892.

<sup>15</sup> Riv. sper. di fren., 1900, p. 468.

<sup>16</sup> Beitr. z. path. Anat. u. z. allg. Path., 1898, 23, 90.

<sup>17</sup> AM. JOUR. MED. SCI., 1911, 141, 374, 535.

<sup>18</sup> Beiträge zur Pathologie und Pathogenese der Akromegalie, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, 20, 620-644.

<sup>19</sup> Loc. cit., pp. 280-281.

<sup>20</sup> Ueber den Hirnanhang fallsüchtiger Personen, Mainz, 1810.

<sup>21</sup> Beiträge zur Lehre von den Geschwülsten innerhalb der Schädelhöhle, Wurzburg, 1853.

<sup>22</sup> AM. JOUR. MED. SCI., March, 1913, p. 313.

<sup>23</sup> Volkmann's klin. Vortr., 1899, p. 242.

megaly and myxedema, as shown, he believes, by the comparatively frequent coexistence of the two conditions, by the similarity of many of the symptoms and by the occurrence of similar pathological changes in the two conditions. Without doubt these two glands exhibit points of resemblance both from a histological and a physiological viewpoint, so that their commonly observed clinical association should be expected. To show the similarity of their effects upon metabolism it is only necessary to call attention to the fact that myxedema occurring before the growth of the bones is completed causes an arrest of ossification. Functional associations between the pituitary, adrenal, thymus, pineal and genital glands are also recognized, but these will not receive consideration here for want of space.

Whether in the cases of associated changes in the pituitary and thyroid the latter shows atrophy or hypertrophy in the majority of the cases is, perhaps, no longer a moot question (*vide. infra*). For example, Schönemann<sup>24</sup> believes that an increase of hypophysis may take place in cases of hypertrophy of the thyroid gland; he has, however, "failed to find any compensatory increase of the hypophysis in goiter—that is, in cases of degeneration of the thyroid or in cachexia strumipriva." On the other hand, Souza-Leite,<sup>25</sup> based on an extensive collection of cases, holds that an atrophy of the thyroid is more frequently associated with an enlarged hypophysis than hypertrophy of the thyroid. Hutchinson<sup>26</sup> affirms that the thyroid is atrophied in about 10 per cent of all cases of acromegaly and enlarged in 30 per cent, the enlargement being due usually to cystic degeneration.

It would appear that practically all of the larger earlier post-mortem reports of fatal myxedema in which the hypophysis was examined no abnormalities were observed. We venture to believe, however, that solitary instances of the association of lesions under discussion is decidedly more common than was formerly supposed. Moderate increase in size and microscopical structural changes which are not infrequently present are easily overlooked unless the examinations be thorough and complete.

The effects of hyperactivity of the anterior hypophysis differs in different cases with alterations in the functions of the other internal glands, more particularly the thyroid gland. In this connection the observation of Berkeley<sup>27</sup> that the anterior lobe of the hypophysis is abundantly supplied with sympathetic fibers while the posterior lobe is devoid of such fibers, goes far toward explaining the interrelation between diseases of the former and hyper- and hypothyroidism.

<sup>24</sup> Quoted by Boyce and Beadles: Loc. cit.

<sup>25</sup> L'Acromegalie, Paris, 1890.

<sup>26</sup> New York Med. Jour., 1898, No. 11, vol. 67.

<sup>27</sup> Quoted by Bell, p. 32.



In a previous paper by us<sup>28</sup> the purpose was, among other things, to collect all cases of pituitary disease recorded in literature covering a period of five years terminating December 31, 1913, and to aid in clearing the question of the relation of hypo- and hyperthyroidism to acromegaly on the one hand and glycosuria on the other. In 5 out of 16 cases (31.5 per cent) of acromegaly in which the thyroid was reported on changes were noted. Of these the thyroid was small in 1, normal in 1, sclerotic and cystic in 1, not palpable in 1, while the remaining case (our own) showed well-marked evidences of hyperthyroidism. These figures would appear to show that the role played by hyperthyroidism in cases of acromegaly is trivial and uncertain. On the other hand they indicate that hypothyroidism is more commonly found in association with pituitary disease.

It is of much interest to note that while acromegaly is regarded as being a rare disease, six years after Marie<sup>29</sup> first described the condition Collins<sup>30</sup> was able to collect about 90 cases from the literature. In 1898 Hinsdale<sup>31</sup> found reports of 130 cases, of which 23 showed exophthalmos, and in the same year Woods Hutchinson collected 218 cases.

In 1893 James J. Putman<sup>32</sup> treated a case of acromegaly with thyroid powder (gr. xv every second day); the condition improved markedly, the enlargement of the hands and feet having practically disappeared. We believe it is safe to infer that in this instance hypothyroidism was associated and that the hypertrophy affected principally the soft tissues. Putman refers briefly to 2 additional cases, "The one stands nearer to acromegaly and the other to myxedema, though in both the diagnosis is doubtful." Both were given thyroids with excellent results. In the former there was a large swelling of the neck, "probably a thyroid, which is diminishing under thyroid extract." There can be but little doubt that this was an instance of combined pituitary and thyroid disease, since hypothyroidism is known to occur in subjects showing enlargement of the gland. Such cases we believe are common examples of advancing hypopituitarism associated with hypothyroidism. They are, as a rule, greatly benefited by careful glandular therapy.

On the other hand Burns's, Benson's and Mosse's cases (quoted by Hinsdale) treated with thyroid extract showed improvement principally in the subjective symptoms, more particularly in the nervous phenomena, without diminution in the size of either the lips, hands or feet. In such an absolute diagnosis of an associated hypothyroidism would be unwarranted. In this connection it is to be borne in mind that in myxedema the hypertrophy affects the

<sup>28</sup> AM. JOUR. MED. SCI., 1914, 147, 323.

<sup>29</sup> Revue de Méd., 1886.

<sup>30</sup> Jour. Ment. Nerv. and Dis., 1892.

<sup>31</sup> Acromegaly, 1898, p. 23.

<sup>32</sup> Tr. Aesn. Am. Phys., 1893, 8, 338.

soft tissues exclusively, although the basal metabolism, especially as related to the nervous system, is decreased in this disease. Improvement in the mental condition, however, in the absence of a favorable effect upon the soft tissues in myxedema is contrary to universal experience

The growing tendency to regard individual cases of glandular disease as being of pluriglandular origin is unjustified. As pointed out by Falta<sup>33</sup> in speaking of pathological correlation, "The disease that has first involved one gland involves in its further course other members of the ductless glandular system." True it is that upon close analysis of the history, symptoms and course of a given case it is quite frequently possible to discern which ductless gland was first affected.

Secondary to primary involvement of the hypophysis the symptomatic indications of both hypo- and hyperactivity of the thyroid may arise. That the converse may obtain, however, seems to be supported by ample evidence, *e. g.*, in certain cases of Graves's disease. Bell<sup>34</sup> has studied the pituitary in disease of the thyroid. He described the results of a histological examination in a case of cretinism in a female who died at the age of thirty-three years; the structural characteristics found indicated considerable activity, which he thinks were probably compensatory in character.

In exophthalmic goiter many more basophils than is normal are found in the pars anterior, while in the pars posterior the number is normal. Certain it is, however, that reliable deductions must await further information concerning secondary pluriglandular effects. At all events it would seem to us highly probable that the effect upon the pituitary (anterior lobe and intermedia) is more marked after the removal of the thyroid than after the removal of other hormonopoietic organs.

Friedman<sup>35</sup> claims there is a certain degree of hypophyseal hyperactivity in hyperthyroid and of hypoactivity of the pituitary in hypothyroid states. If this be true, then, pituitary products are contraindicated in the treatment of Graves's disease, but indicated in addition to thyroid in myxedematous subjects. This dictum receives confirmation from the histological studies of the hypophysis in hyperthyroidism and myxedema by Fry,<sup>36</sup> who points out that in the former condition the histology corresponds to a gland of high activity and in the latter to a gland of low activity. The pituitary in myxedema is anatomically a hypertrophied gland, but physiologically an atrophied one.

It is especially in these hybrids that mild forms of hypothyroidism, which are so difficult to diagnosticate, are liable to occur; but

<sup>33</sup> The Ductless Glandular Diseases, second edition, p. 440.

<sup>34</sup> The Pituitary, William Wood & Co., New York, p. 262.

<sup>35</sup> Loc. cit.

<sup>36</sup> Quart. Jour. Med., 1914-15, 3, 277.

their recognition is important, as shown by the happy effects of metabolic stimulation by means of thyroid extract so far as the myxedematous manifestations are concerned. As elsewhere stated by one of us:<sup>37</sup> "In both the skin is dry; the subcutaneous fibrous connective tissue is thickened by overgrowth; the tongue is enlarged; the mucous membranes, especially of the nose, soft palate and uvula, are thickened; and menstrual disorders in the female; in both there is irritability of temper, slowness of the mental processes and thick, difficult speech."

Certain obvious features, however, belong to each of these diseases alone when found to be combined. For example, the general bony enlargement with separation of the condyles, spreading apart of the teeth, increased growth of the hair on the head, enlarged joints, the severe headaches and increased muscular strength followed by muscular weakness; in women hairiness assuming the male type, disturbances of vision and bilateral hemianopsia are dependent on the acromegaly; while the tendency to chilling, a subnormal temperature, diminished metabolism, elastic skin—dry and scaly (no pittings)—miniature thyroid, malar flushes, loss of hair, slow small pulse, often arteriosclerosis and slight albuminuria, as well as a peculiarly distorted physiognomy (masked facies), belong to myxedema. Attention should be directed here to those minor forms in which the symptoms are merely suggestive of associated hypothyroidism. In such the cautious use of thyroxin is advised in order to confirm the diagnosis.

In associated hyperthyroidism the cardinal symptoms, such as tachycardia, tremor, exophthalmos, nervousness, increased sweating and increased metabolism, may be more or less frankly expressed, in which case an assured diagnosis is beyond question. In certain cases the degree of hyperthyroidism is moderate or even slight and the symptoms presented are indefinite and variable. Slight tachycardia, a moist delicate skin, a tendency to diarrhea, often polyuria, amenorrhea, slight increase in size of the thyroid, and somewhat widened palpebral fissures and an increased metabolic rate, which is a reliable criterion, are among the most significant diagnostic features in these mild, atypical forms. In the sympathicotonic type one may observe exophthalmos with tachycardia, but no sweats or diarrhea, marked falling out of the hair or alimentary glycosuria.

In this connection Janney's<sup>38</sup> view that the classic symptoms of exophthalmic goiter are of toxic origin or due to a perverted rather than to mere excess of thyroid secretion is to be recollected. If we accept this theory we shall be in a position to appreciate how toxic and hypothyroid symptoms may be combined in a given case. Again, in cases of acromegaly with associated exophthalmic goiter

<sup>37</sup> Anders: *Diagnosis of Myxedema*, *AM JOUR. MED. SCI.*, 1920, 160, 801.

<sup>38</sup> *Arch. Int. Med.*, August, 1918, p. 187.

and deficiency symptoms small doses of thyroid extract may prove useful while larger ones would produce an unfavorable effect. Before forming a final diagnostic opinion, however, exophthalmos due to the pressure effects of the hypophyseal enlargement must be eliminated. It is to be recollected that a state of thyroid insufficiency following hypophyseal overactivity is not reached before death in all cases, but only in those in which degenerative changes occur.

An examination of the literature reveals not a few cases of combined pituitary and thyroid disease in which the manifestations of hypothyroidism overshadow those of hypophyseal disease. To overlook the true nature of these is unfortunate in view of the happy effects of appropriate glandular therapy. We have personally observed modifications of the function of the thyroid in two cases of acromegaly, which are here briefly detailed:

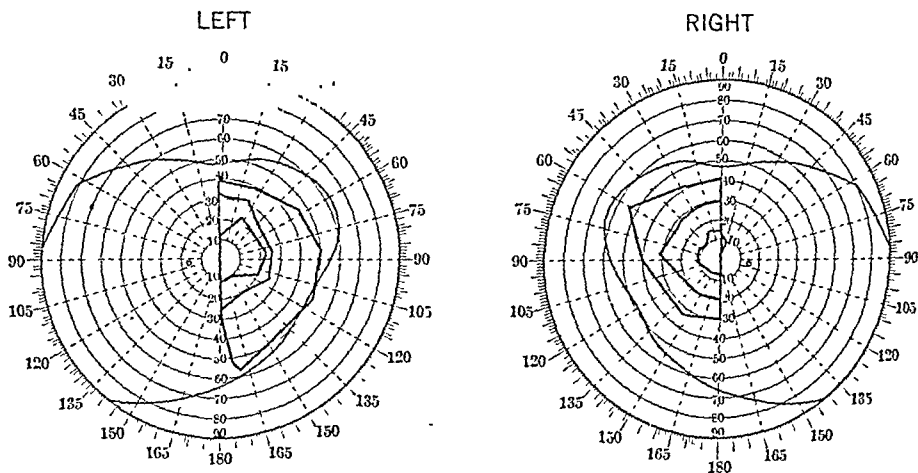
CASE I.—A. J. M., female, aged thirty-four years; single; weight, 168 pounds; teacher in the public schools; was referred to one of us for study and treatment by Dr. S. Lewis Ziegler, November 3, 1917. The paternal grandfather died of apoplexy, also the maternal grandfather. The patient had some of the childish diseases and during adolescence repeated attacks of tonsillitis. Eight years ago she was operated on for tuberculosis of the "right tube and ovary"; the wound is still unhealed (fecal fistula). The patient had been taking little exercise and menstruation had always been delayed and scanty, followed by amenorrhea during the past fourteen years. For a long time she had been constipated and complained of nervousness, irritability and was annoyed by any noise; during the past year she had much headache and always felt chilly. During the past two years she noticed a divergence of the left eye, and states that for about eight years she had large bones.

*Status Praesens.* Bones of face, hands and feet as well as those of the trunk unusually large; hands and feet especially broad in bony parts, spade-like; lower jaw prognathus. Complains of severe headaches at times with nervousness and marked irritability of temper; speech is slow, thick and leathery.

Myxedematous infiltration of the skin of the face and extremities is present, but had not been previously recognized. An associated symptomatic anemia is more marked than usual. For example a blood count showed erythrocytes, 3,110,000; leukocytes, 6000; color index, .9; hemoglobin, 55 per cent. The skin exhibits a slightly yellowish hue with marked pallor of the mucous membranes. The thorax is negative; a fecal fistula is noted in the right lower quadrant of the abdomen. The thyroid is not palpable. The urine proved negative and there is increased sugar tolerance.

Dr. Ziegler reports eye-findings as follows: "She first noticed diplopia about one year ago, which doubtless was caused by the

muscular error in her eyes, which amounts to a hyperphoria of 4 degrees and an exophoria varying from P 18 degrees to P 20 degrees. Her refraction is compound hypermetropic astigmatism of low grade. I have corrected the hyperphoria, but cannot correct the exophoria without again causing her diplopia, as one eye wanders off far enough to limit her to monocular vision. The nerve head shows slight pallor on the temporal side. The fields are absolutely hemianopic with some contraction, as is indicated in the charts of the same, which I enclose."



A roentgen-ray study by Dr. G. E. Pfahler follows: "I find great thickening of the skull. The cranial vault is approximately 2 cm. in thickness—three or four times as thick as normal. There is a tumor in the region of the pituitary and this tumor has extended both upward above the sella and has broken through the floor of the sella, extending into the region of the sphenoid. This is the first time that I have seen such a condition (in which the tumor has extended through the floor). The clinoid processes are not widely separated or destroyed, as is commonly the case, probably due to the fact that the tumor has extended downward more than upward. The hands show the thickening about the ends of the distal phalanges, and in fact general thickening about the ends of all of the phalanges and of all of the metacarpals. They have the appearance that we commonly find in acromegaly." The case is looked upon as one of acromegaly with associated myxedema and tuberculosis.

The use of thyroid extract in small doses has been remarkably effective for good. Not only has there been a marked subsidence of all of the myxedematous features, but the headaches, speech and nervous irritability have also been greatly relieved. The bony skeleton, however, has remained stationary.

CASE II.—A. H., aged forty-six years, female, occupation cook, weight 170 pounds, height 5 feet 9½ inches, first came under the care of our surgical colleague, Dr. William L. Rodman, in the Medico-Chirurgical Hospital, December 5, 1913, at which time she was suffering from a gangrenous wound, inflicted by a fish-bone, of the left hand. A few days later the patient was referred to the medical service (to us) for study and treatment. Polydipsia, polyuria and glycosuria, as well as bulimia, were all prominent features throughout the illness. The percentage of sugar at first was 5 per cent, but at the end of one week it rose gradually to 7 per cent, and remained at this level until the end.

The typical symptoms of acromegaly were in evidence. According to the history the bones of the hands and face began to enlarge four years ago while the glycosuria set in about two years later. A roentgen-ray examination by Dr. Pfahler showed marked lipping at the edges of the articular surfaces of the metacarpal bones and phalanges, such as is found in acromegaly, and also a tumor of the pituitary gland, with absorption of the clinoid processes. The diagnosis of associated hyperthyroidism was quite apparent from the noticeable enlargement of the thyroid gland, together with tremor, tachycardia and exophthalmos. The indications of exophthalmic goiter were most probably developed after the glycosuria had existed for an indefinite period of time, although being, as is usual, of insidious origin, it was impossible to fix the precise date of onset. The Wassermann reaction gave a negative result.<sup>39</sup>

With a view of indicating the true pathological relationship between disease of the hypophysis and thyroid the results of a statistical study are subjoined. The total number of cases collected by us, which was 215, includes only a few that were reported prior to the publication of the paper of Dr. Hinsdale in 1898 and that of Hutchinson in 1902. Table I is a detailed tabulation of 91 cases in which thyroid disturbance was associated.

It should be pointed out that the notations to be found in the columns headed hyper- and hypothyroidism are the inferences drawn by the original reporters, with few exceptions. Failure to record the sugar tolerance and condition of the thyroid gland and its function in numerous cases is to be regretted. It is interesting to note that all of our series, or 215 cases, occurred in the white race with a single exception, which was reported by Yamada, of Tokio (*vide* Table I). Trauma played a role in 3 cases and in 2 the disease followed "psychic trauma." According to these findings the influence of traumatism as a disposing factor is insignificant. There can be no doubt but that a family type exists, although the influence of heredity must, on the whole, be trivial, as evidenced by our results, namely, two instances only of the entire series.

<sup>39</sup> This case is more fully reported in a previous article by Anders and Jameson, *loc. cit.*

TABLE I

Reporter.	Reference.	Age.	Sex.	Lesions in thyroid.	Hyperthyroidism.	Hypothyroidism.	Lesions in pituitary.	Glycosuria.	Remarks.
Lancereux	Semaine m <sup>é</sup> d., 1895, xv, 61	40	F	Hypertrophy	Present	....	....	Present	Trauma.
Henrot	Quoted by Lancereux, loc. cit.	36	M	Goiter	Present	....	Tumor size of hen's egg	Present	Reported in 1877; heart hypertrophied.
Valat	Idem.	..	..	Goiter	Present	....	....	....	Reported in 1893.
Haskovec	Wien. klin. Rundschau, 1895, ix, 257	35	M	Atrophy	....	....	....	Absent	Head injury followed by meningitis.
Sears	Boston Med. and Surg. Jour., 1896, cxxxv, 16	45	F	....	....	Present	....	Absent	Improved by thyroid administration.
Dodgson	British Med. Jour., 1896, i, 660	23	F	Enlarged	....	Marked	Sarcoma with psammomatous degeneration	....	Myxedema disappeared under thyroid treatment.
Worcester	Boston Med. and Surg. Jour., 1896, cxxxiv, 413	70	F	Not palpable	....	....	Adenoma-cystic degeneration	....	....
Furnival	Lancet, London, 1897, ii, 1190	58	M	Slightly enlarged and altered in function	....	Present	Sarcoma or hypertrophy and posterior lobe almost disappeared	Present	Thymus normal.
Dalton	Idem.	..	..	Normal, except thyroid juice unusually fluid	..	Present	....	Present	....
Murray	Edinburgh Med. Jour., 1897, i, 170	37	F	Goiter	Present	....	....	Present	Pulmonary tuberculosis.
Murray	Idem.	63	F	Large cystic goiter	Absent	....	..	Absent	....
Murray	Idem.	34	F	Enlarged	Present	....	Enlarged	Present	Pulmonary tuberculosis; thymus hypertrophied.
Schiff	Wien. klin. Wchnschr., 1897, x, 277	37	M	....	....	Present	....	Increased tolerance	....

Schiff	Ztschr. f. klin. Med., 1897, xxii, 289, Suppl.	..	..	....	Present	....	....	....	Unable to consult article
Osborne	Tr. Assn. Am. Phys., 1897, xii, 262	47	M	Enlarged 101 gm., extrathyroid in chest, 36½ gm.	....	....	Sarcoma (?)	....	Heart enormous.
Comte	Beitr. z. path. Anat. u. z. allg. Path., 1898, xxiii, 90	46	F	Much enlarged	Present	....	Enlarged 0.415 gm.	....	
Comte	Idem.	32	F	Enlarged 330 gm.	Present	Absent	Enlarged 0.85 gm.	....	
Bailey	Philadelphia Med. Jour., 1898, i, 789	65	F	Parenchymatous hypertrophy; nearly 3 times normal weight	....	....	Adenoma	....	
Hunter	Tr. Path. Soc., London, 1898, xlix, 246	52	M	Hypertrophy	....	....	Hypertrophy	....	
Neal	Ibid., p. 237	41	F	Parenchymatous goiter 6½ oz.	Absent	....	Hypertrophy	....	Slight improvement under thyroid.
Coe	Jour. Am. Med. Assn., 1898, xxi, 1347	68	F	Small	....	....	....	Absent	Homicidal.
Thompson	Med. Press and Circ., London, 1898, n. s., lxxv, 377	19	F	....	Present	....	....	Absent	
Ponfick	Ztschr. f. klin. Med., 1899, vol. i.	47	M	Marked atrophy	....	Present	Chronic interstitial inflammation and atrophy	....	
Lediard	British Med. Jour., 1903, i, 789	43	F	Bilateral goiter (large)	....	....	....	Previous glycosuria	Left lobe removed with improvement in pressure symptoms.
Cattle	Ibid., p. 780	30	F	Goiter	Present	....	....	Absent	Exophthalmos, tachycardia and excessive sweating.
Snell	Ibid., ii, 131	38	F	Not enlarged	....	Present	....	Absent	Improved under thyroid treatment.
Launois and Roy	Nouv. iconog. de la Salpêtrière, Paris, 1903, xvi, 163	36	M	Hypertrophy; 250 gm.	....	....	Large epithelioma	Present	



TABLE I.—(Continued.)

Reporter.	Reference	Age, Sex.	Lesions in thyroid.	Hyperthyroidism.	Hypothyroidism.	Lesions in pituitary.	Glycosuria.	Remarks.
Heising	Wisconsin Med. Jour., 1903-04, ii, 684	38 F	Small	....	....	....	....	Preceded by severe psychic trauma; thymus persistent.
Bate	Louisville Month. Jour. Med. and Surg., 1903-04, x, 374	28 F	....	Probable	....	....	....	Attributes tachycardia (100) to overaction of thyroid-like tissue in pituitary.
Salomon	Berl. klin. Wehnschr., 1904, xli, 635	49 M	....	Probable	....	....	....	Increased metabolism; skin resembles myxedema.
Salomon	Idem.	42 M	....	Present	....	....	....	Increased metabolism; skin resembles myxedema; marked arteriosclerosis.
Greene	New York Med. Jour., October, 1905, p. 846	25 M	Small	....	Present	....	Absent	Myxedema disappeared under treatment.
King	South. California Pract., 1905, xx, 410	37 M	....	Absent	Previous myxedema Probable	....	Absent	
Kerry	Ophth. Rev., London, 1905, xxiv, 193	50 M	....	....	....	....	....	Marked improvement under thyroid treatment.
Ballet and Laignel Lavastine	Nouv. iconog. de la Salpêtrière, Paris, 1905, xviii, 176	70 F	Hyperplasia	....	....	Parenchymatous hypertrophy	....	Hyperplasia of adrenals
Taylor	W. London Med. Jour., 1905, x, 124	34 F	....	....	Probable	....	....	Sent as case of myxedema.
Schoenborn	Beitr. z. path. Anat. u. z. allg. Path., 1905, Suppl., vii, 468	65 M	Cystic goiter with interstitial inflammation	....	....	Adenoma size of walnut	Absent	Cardiorenal asthma.
Porter	Ophth. Rec., Chicago, 1906, xv, 207	47 F	Greatly enlarged	Present	....	....	....	

Current	Maritime Med. News, Halifax, 1907, xix, 98	20	F	"Thickening in region of thy- roid"	Present	....	....	....	Improved by pituitary treatment; atrophy of ovaries and uterus. Thymus persistent.
Haywood	Homeopathic Eye Jour., 1907, xiii, 48	33	F	....	Present	....	....	....	....
Sainton and Rathery	Soc. méd. d. hôp., Paris, 1908, xxv, 647	32	F	Atrophy and sclerosis	....	Present	Malignant tumor	Absent	
Renon and Delille	Ibid., p. 973	47	F	....	....	Present	Tumor	Absent	
Kocher	Deutsch. Ztschr. f. Chir., Leipsig, 1909, c, 13	30	F	Small	....	....	Sarcoma	Present	Thymus persistent; op- eration.
Carmody	Lancet, London, 1909, i, 1599	33	F	Previous goiter	....	....	....	Absent	Skin thick but could be pinched, now abnorm- ally active; no improve- ment under pituitary treatment.
Exner	Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, xx, 620	30	F	Enlarged after operation on pituitary	....	....	Malignant ade- noma	Tolerance increased	Tongue, lips, hands and feet smaller after oper- ation.
Exner	Idem.	34	F	Isthmus became size of walnut after operation	....	....	Malignant ade- noma	Tolerance increased	
Packard	Am. Med., 1910, n. s., v, 539	36	F	Hypertrophy	....	....	X-ray unable to demonstrate tumor		
Grove	Bull. Johns Hopkins Hosp., 1910, xxi, 290	47	F	Colloid goiter	....	Present	Enlarged	Absent	Partial thyroidectomy.
East	Jour. Mental Sci., 1912, lviii, 631	43	F	Enlarged	....	....	....	....	Mental symptoms.
Cushing	Pituitary Body and its Disorders, Philadel- phia, 1912, p. 30	35	M	Small	Absent	Absent	Adenoma	....	Ac. secondary to gigant- ism; exophthalmos due to neighborhood pressure.
Cushing Cushing	Ibid., p. 36 Ibid., p. 85	26 36	F M	Colloid goiter Large and col- loid	Absent Absent	Absent Absent	Adenoma Tumor	....	Slight acromegaly fol- lowed by hypopitui- tarism; trauma.

TABLE I.—(Continued.)

Reporter.	Reference.	Age.	Sex.	Lesions in thyroid.	Hyperthyroidism.	Hypothyroidism.	Lesions in pituitary.	Glycosuria.	Remarks.
Cushing	Ibid., p. 137	40	M	Slightly enlarged	Absent	Absent	Slight enlargement of sella turcica	.....	Hypertrichosis.
Cushing	Ibid., p. 140	38	M	Colloid goiter	Absent	Absent	Chromophil-struma	.....	Goiter removed. Benefited by thyroid treatment; complicated by gigantism, hay fever and tuberculous adenitis.
Cushing	Ibid., p. 150	59	M	"Plunging goiter"	Former	Absent	Enlarged	.....	Benefited by thyroid treatment; complicated by gigantism, hay fever and tuberculous adenitis.
Cushing	Ibid., p. 154	42	M	"Possibly enlarged"	Absent	Probable	.....	.....	Secondary to hydrocephalus.
Cushing	Ibid., p. 194	33	M	Enlarged; excess of colloid	Absent	Absent	"Functional hyperplastic change" Sella turcica enlarged	.....	Improved under thyroid treatment.
Holmes	Proc. Roy. Soc. Med., London, 1912-13, vol. vi, Neurol. Ophth. Sect., X	36	F	....	....	Probable	Sella turcica enlarged	.....	Improved under thyroid treatment.
Garrod	Ibid., lxxviii	..	..	....	....	Present	Sella turcica enlarged	.....	Improved under thyroid.
Brown	Ibid., lxxvii	40	F	Cystic goiter	....	"Possible myxedema"	....	Tolerance increased	Previous acromegaly; now hypopituitarism; some improvement under thyroid.
Bartlett	Tr. Chicago Path. Soc., 1913, ix, 56	25	M	Colloid goiter	....	....	Chromophil-cell adenoma	.....	Thymus persistent.
Gordinier and Kirk	Albany Med. Ann., 1913, xxxiv, 189	39	F	Distinctly enlarged	....	..	Tumor	.....	Followed infected vaccination and psychic trauma; benefited by thyroid; epilepsy.
Gruker	Jour. Am. Med. Assn., 1913, lvi, 235	49	M	Absent	....	Present	Large adenoma	Intermittent	

Millioni	Riforma med., Naples, 1913, Nos. 39, 40 and 41, vol. xxix	34	F	Small	....	Present	Marked enlargement; probably tumor	Absent	
Fernsides	Proc. Roy. Soc. Med., London, 1913-14, vii; Electro-therap. Sect., 46	40	F	Not palpable	....	Present			
Dunn	Am. Jour. Med. Sci., 1914, cxlviii, 214	61	M	Small	....	....	....	Tolerance increased	Hemoptysis; non-tuberculous; angioneurotic edema.
Anders and Jameson	Ibid., p. 323	46	F	Goiter	Present	....	Tumor	Present	Gangrene.
Osborne	Proc. Connecticut State Med. Soc., 1914, p. 164	40	M	....	....	Present			
Chizet	Lyon méd., 1914, cxvii, 882	15½	M	....	....	Present	Tumor	....	Polyuria.
Bendell	Albany Med. Ann., 1915, xxxvi, 441	45	F	Colloid enlargement					
Furth	Med. klin. Berl., 1915, xi, 1347	40	F	Palpation negative	....	Deficient iodine production	Tumor	....	Temporary improvement under iodide treatment, father had goiter.
Falta	Ductless Glandular Diseases, Philadelphia, 1916, p. 237	32	M	Enlarged	....	....	....	Tolerance increased	Heart enlarged; hypertrichosis.
Falta	Ibid., p. 243	31	M	Slightly enlarged	....	....	....	Tolerance increased	Hypertrichosis.
Falta	Ibid., p. 243	31	M	Not enlarged	Probable	....	Adenoma	....	Hypertrichosis; thyroid in aggravated symptoms; temporary improvement after operation.
Falta	Ibid., p. 246	33	F	Enlarged	....	....	....	Tolerance decreased	Marked hypertrichosis; lues.
Falta	Ibid., p. 253	37	F	....	Present	....	Grayish-red tumor	Tolerance decreased	
Falta	Ibid., p. 266	31	F	....	Present	Present	....	Tolerance decreased	Hyper-followed by hypothyroidism.

TABLE I.—(Continued.)

Reporter.	Reference.	Age.	Sex.	Lesions, n thyroid.	Hyperthy-roidism.	Hypothy-roidism.	Lesions in pituitary.	Glycosurin.	Remarks.
Fletcher	Med. Clin. North Amer- ica, 1917, i, 131	67	F	....	Absent	Possible associa- tion of myx- edema	Sella turcica en- larged	Tolerance increased	Possible early paralysis agitans.
Soner	Med. Jour. So. Africa, 1918, xiii, 102	34	F	....	Absent	Present	....	....	Improved under thyroid treatment.
Yamada	Mitt. a. d. Med. Fac. d. k. Univ. z. Tokyo, 1918, viii, 411	17	M	Hypertrophy	....	....	....	....	Thymus persistent; died of beriberi.
Good and Ellis	Endocrinology, 1918, ii, 431	58	M	Atrophy	....	Present	Hemangio- endothelioma	Tolerance increased	Thymus persistent; tes- tes and adrenals atro- phied and sclerotic.
Lewis	Laryngoscope, 1918, xxviii, 604	34	F	....	....	Present	....	....	Pulmonary tuberculosis.
Loewenberg	Internat. Clinics, 1918, 28th ser., iii, 154	34	M	Slightly enlarged	....	....	Tumor (calcified)	....	Developed copious milk secretion.
Roth	Berl. klin. Wchnschr., 1918, lv, 305	28	M	Enlarged	....	....	Tumor	Absent	
Howard	Am. Jour. Med. Sc., 1919, clviii, 830	31	M	Slight cystic de- generation	....	Probable	Round-cell sarcoma	Tolerance increased	
Howard Webster	Idem.	47	F	Slight goiter	Probable	....	....	Present	Headaches relieved by x-ray.
	Arch. Radiol. and Elec- tro., London, 1919-20, xiv, 261	..	..	Enlarged	....	....	....	Tolerance increased	
Tierney	Med. Clin. North Amer- ica, 1920, No. 3, iv, 799	40	M	Enlarged	....	....	....	Tolerance increased	Father and sister acro- megalic types.
Barr	New York Med. Jour., 1920, cxi, 218	36	M	Enlarged	....	....	Sarcoma	....	Imbecile.
Bernstein	Not published	39	M	Small	....	Probable	Large adenoma	Tolerance increased	Operation relieved head- ache, preserved vision; acromegaly stationary since.
Anders and Jameson	Not previously pub- lished	34	F	Small	....	Present	Tumor	Tolerance increased	Improved by thyroid treatment.

TABLE II.—TOTAL CASES OF ACROMEGALY, 215

Age (cases mentioned, 195).		Sex (cases mentioned, 194).		Lesions of pituitary (cases mentioned, 99).	Lesions of thyroid (cases mentioned, 68).	Glycosuria (cases mentioned, 91).	
Male.	Female.	Males.	Females.			Present.	Absent.
37.14	38.76	90 (46.4 per cent)	104 (53.6 per cent)	"Tumor" . . . 41 Adenoma . . . 15 Sarcoma . . . 12 Sella turcica enlarged 13 Enlarged . . . 6 Hypertrophy . . . 3 Various . . . 9	Enlarged . . . 24 Goiter . . . 20 Atrophy . . . 17 Hypertrophy . . . 7 Functional . . . 23	32 (35.2 per cent)	59 (64.8 per cent)
Average age, 38.3							

TABLE III.—COMBINED ACROMEGALY AND THYROID DISTURBANCE, 91 CASES

Age (cases mentioned, 86).		Sex (cases mentioned, 86).		Lesions of pituitary (cases mentioned, 47).	Lesions of thyroid (cases mentioned, 68).	Glycosuria (cases mentioned, 47).	
Male.	Female.	Males.	Females.			Present.	Absent.
39.64	39.98	37 (43 per cent)	49 (57 per cent)	"Tumor" . . . 13 Adenoma . . . 11 Sarcoma . . . 6 Enlarged . . . 4 Sella turcica enlarged 4 Hypertrophy . . . 3 Various . . . 6	Enlarged . . . 24 Goiter . . . 20 Atrophy . . . 17 Hypertrophy . . . 7 Functional . . . 23	14 (30 per cent)	33 (70 per cent)
Average age, 39.85							

TABLE IV. — ACROMEGALY WITHOUT THYROID DISTURBANCE, 124 CASES

Age (cases mentioned, 100).		Sex (cases mentioned, 108).		Lesions of pituitary (cases mentioned, 52).	Glycosuria (cases mentioned, 44).	
Male.	Female.	Males.	Females.		Present.	Absent.
35.4	37.07	53 (49 per cent)	55 (51 per cent)	"Tumor" . . . . . 28 Sella turcica enlarged . . . . . 9 Sarcoma . . . . . 6 Adenoma . . . . . 4 Cyst . . . . . 2 Enlarged . . . . . 2 Degeneration . . . . . 1	18 (41 per cent)	26 (59 per cent)
Average age, 37.18						

A review of Table II shows that in 99 cases out of the 215 cases of acromegaly the lesions of the pituitary are mentioned and that in 68 cases thyroid changes are recorded. It is noteworthy that only three more examples of adenomata than sarcomata are reported among the pituitary lesions, it being currently stated by the older as well as recent writers that the great majority of the new growths of this gland in acromegaly are adenomata. The influence of sex upon the incidence of the disease is shown by a slight preponderance in favor of the female. On the other hand Hinsdale's figures indicate that the disease is more common in the male than in the female sex; for example, he found 73 males and 57 females in his series of 130 cases. The average age here given (thirty-eight and three-tenth years), which represents that of the ages reached at the time the cases were reported, is too high, but the date of onset was so frequently indeterminable from the histories recorded in the literature as to make this course necessary. Table III needs no description.

Table IV shows the age incidence to be slightly higher in the combined pituitary and thyroid cases than in the uncombined acromegalics and also a slightly greater preponderance in the female as compared with the male sex by comparison with acromegaly without associated thyroid lesions. It cannot be stated, however, that these figures afford a basis for the claim often advanced that the thyroid is a true sex gland, as is shown by both Graves's disease and myxedema when they occur independently of the acromegaly. For example, both the latter conditions are six to eight times as frequent in the female as in the male. It will be noted that the proportion of cases of adenoma in Table IV as compared with sarcoma is almost three times greater than in Table III, although the figures are too small on which to base any inferences.

TABLE V.—AGE BY DECADES

Acromegaly without thyroid disturbance.		Acromegaly with thyroid disturbance.	
Under 20 years	3	Under 20 years	3
21 to 30 "	32	21 to 30 "	7
31 to 40 "	34	31 to 40 "	39
41 to 50 "	17	41 to 50 "	25
51 to 60 "	18	51 to 60 "	4
61 to 70 "	4	61 to 70 "	6
71 to 80 "	1	71 to 80 "	2

An inspection of Table V, which presents the age incidence by decades, will show that for acromegaly with associated thyroid disturbance this is considerably higher than in the cases without involvement of the thyroid—an interesting fact. The explanation is probably to be found in the accepted view that thyroid complaints, myxedema in particular, develop later in life than uncomplicated acromegaly, as a rule. This table indicates clearly that



the great majority of cases of acromegaly with thyroid disturbance arise between the thirtieth and fiftieth years of age, and that both during the decade prior to that period of life and subsequently the cases are far less numerous than in acromegaly without thyroid disturbance. Again, it should be noted that in the cases of acromegaly in which thyroid disturbance is combined the latter usually arises a number of years after the onset of the former, *i. e.*, when the stage of hypopituitarism is reached.

TABLE VI.—THYROID FUNCTION, 52 CASES

Hyperthyroidism, 20 (38.5 per cent.)		Hypothyroidism, 32 (61.5 per cent.)	
Male . . . . .	5	Male . . . . .	12
Female . . . . .	14	Female . . . . .	18
Glycosuria.		Glycosuria.	
Present . . . . .	7	Present . . . . .	2
Absent or increased tolerance	1	Absent or increased tolerance	16

Table VI exhibits the facts bearing on the relative incidence of hyper- and hypothyroidism and on the carbohydrate tolerance as well as the influence of sex on the thyroid function. It will be seen that in the hyperthyroid group the ratio in favor of the female is about 3 to 1 while in the hypothyroid cases it is 3 to 2. Again, the incidence of hypothyroidism as compared with that of hyperthyroidism is about as 3 to 2. With regard to the question of carbohydrate tolerance in cases of combined acromegaly and disturbed thyroid function Table VI demonstrates that in hyperthyroidism the sugar tolerance was decreased in 7 out of 8 cases—ratio 7 to 1. On the other hand in the cases of associated hypothyroidism sugar was absent or tolerance increased in the ratio of 8 to 1. It should be added that of the 16 cases belonging to the latter group in 7 the increased sugar tolerance was determined by the usual tests.

**Summary.** Our literary studies have revealed an unexpected frequency of associated disturbance of the thyroid function in cases of acromegaly, or 33 per cent, as shown by Table I. It is highly probable that in many instances of pituitary disease with its usual syndrome the coexistence of thyroid alterations and symptoms resulting therefrom were overlooked, as was true of one of the two cases which was reported by us. Our investigations indicate that hypothyroidism is more commonly associated with acromegaly than hyperthyroidism, and that those combined cases which manifest myxedematous features are decidedly improved as the result of the use of thyroid preparations.

It follows that the recognition of the indications of hypothyroidism in connection with acromegaly is a matter of the utmost importance. In cases of acromegaly in which merely suspicious features of either hypo- or hyperthyroidism exist it is strongly urged that

the metabolic rate be determined. The approved sugar tolerance test should be carried out in all cases of acromegaly with a view of determining the state of both the pituitary and the thyroid function. Nothing of special significance bearing upon the etiological factors of the disease under consideration resulted from our studies, with the possible exception of the facts developed in connection with the age groups by decades (*vide* Table V). Our grateful acknowledgements are made to Dr. Andrew A. Anders for valuable assistance in the literary investigations.

## EPILEPTOID OR FAINTING ATTACKS IN HYPOPITUITISM.<sup>1</sup>

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WE shall make no attempt to analyze hypophyseal dysfunctions in their relationship to epileptiform seizures. This has been fairly well done by Cushing, Johnston and others. Nor shall we discuss the reverse influence, as that of clinical epilepsy, upon the hypophysis, as in the studies of Munson at Craig Colony, or take time and space to consider the subjects of syncope and fainting in general. Even so simple a clinical observation as that of fainting probably has a very complicated and varied psychical and somatic mechanism. We do wish, however, to call attention to the fact that there is an increasing accumulation of clinical data of apparently idiopathic attacks of fainting without general somatic defect of the viscera. During the past few years several such cases have been referred to me on the suspicion that these individuals were suffering from a larval form of petit mal epilepsy.

We may enumerate briefly some of the salient differences between this special type of syncope and petit mal epilepsy. We must first note, however, that it is commonly stated that individuals who have their first attacks of petit mal are only suffering from a form of fainting dependent upon some dysfunctions of the viscera, a weak heart or indigestion. In other words, both laity and physicians are much more likely to believe that the early attacks of petit mal are but a form of syncope and in consequence of little moment.

As for real differential diagnosis: If there be no obvious or immediate exciting cause such as emotional stress or physical shock the individual attack of loss of consciousness is more likely to be nothing more than a syncopal one. Slow and incomplete loss of consciousness also is in favor of the state being simply that of fainting. While a sensation of faintness is common to both, usually it takes on much more elaborate characters such as are seen in the epigastric aura. This aura has the sensation of a rising of an inde-

<sup>1</sup> Read before the American Psychopathological Association, June, 1921.

scribable numbing, burning or full feeling which reaches to the level of the chin, when consciousness is always lost in true epilepsy. In simple syncope frequently there is a sense of dizziness, palpitation in or about the heart, and, what is even more frequently encountered, a sinking uneasiness about the heart. When, however, there is no premonitory warning the diagnosis may be very confusing; under such circumstances one needs to think of the state as probable epilepsy, for less than a third of all epileptics have a warning of the approach of their convulsive seizures. In all syncope there is usually an absence of after-effects, which on the contrary are almost invariably present in epilepsy, such as malaise, mental hebitude and mental confusion. In epilepsy there is little pulse alteration, while this is common after pure syncopal attacks. In the absence of a sharp and distinct loss of consciousness one may look at the episodes as being purely syncopal. The presence of any degree of convulsive movement—*independent*, of course, of trembling from sheer weakness—marks the state as almost surely epilepsy as well as any transitory phenomena of automatism, sleep or stupor following the attack. Usually the syncope has so little to do with any phase of true vertigo that the absence of any part of the labyrinthian syndrome usually proves that the latter is playing no role in the state. While the classical types of continued syncopal attacks in dysfunctions of the hypophysis are not so often encountered in any large classical material the atypical instances of the states of fainting are perhaps more frequent. These atypical cases usually present themselves as follows: The general practitioner sees them in the rapidly growing boy or girl in late adolescence. There is a history of insufficient sleep and overindulgence in work, play or social functions. This adolescent has a history of having grown very fast—several inches in height at the puberty period—he is physically too large for his age but, as the eugenic law proves, however, he may be entitled to his extra height by comparing those of the parents; it is his too sudden acquirement of it that is pathological. The boy is soft in muscles, perhaps fatigues easily, may be extra awkward, shy or timid. As not infrequently happens he is rather dull in school-work. The latter defect shows the boy is concrete-minded; is restless and discontented with the school discipline; he wants to evade school duties and prefers an outdoor existence, although he cannot stand continuous outdoor activities without fatigue. Physically the patient also shows labile vasomotor changes; takes cold easily; has cold, dusky hands and feet and unexplainable periods of clammy sweats. Above all, when he gets up suddenly or is required to stand perfectly still he has vague or actual syncopal attacks. The clever physician after noting there is no real organic mischief in the boy's makeup cautions him against too intense physical training, etc., and dismisses the case. Perhaps the physician infers unwisely that the patient's nerves and blood need to be built up and prescribes accordingly. If these drugs

are really potent considerable harm may be done, inasmuch as the youth needs neither more nor richer blood, nor does the nervous system need any stimulation, as the latter is already doing its best to quiet the youth by registering extra fatigue and compelling him to sleep long hours. The physician may wisely follow the main trends of compensation already indicated in the individual patient, that of more moderate but continuous outdoor activity and increased hours of sleep (some patients require twelve to fourteen hours to offset an ordinary day's activity), in which case those milder types never return for treatment. Occasionally, half-fearing the condition is epileptic in type, the physician gives sedatives. For a few days the youth appears better, then he returns, showing increased tendencies to syncopal attacks or he becomes very dull and exhausted. Even small doses of sedatives often produce definite toxic effects. On the patient's return for treatment the physician suspects he has prescribed an overdose of the remedy and either reduces it or takes it away entirely or resorts to additional blood and nerve tonics which seriously complicate the clinical picture. As yet the varied and complicated types of endocrine dysfunctions are so little known and described that the average physician little suspects the varied pictures which ductless gland imbalance may present, and many wait until later, when more pronounced types of the text-book descriptions are evolved. While in a real quandary what to do next the physician begins to sense that his patient has all sorts of things which are on the point of beginning, such as flat-foot, gastropnoia, crooked spine, constipation and skin disorders. Inferring that the youth is on the way to an early dissolution, everyone becomes alarmed. Then ensues a general round of visits to various specialists to do patchwork on the particular anatomical part each may find out of order. One of my patients was visiting six specialists, and his nervous invalidism was much encouraged by his narcissistic concern over these various treatments, which were limited to a half-dozen merely because time did not permit of more.

Many of these slighter grades of hypophyseal dysfunctions cure themselves,<sup>2</sup> or, better, the other ductless glands cure hypophyseal

<sup>2</sup> Apropos of this statement the following case may be cited: A young man, aged twenty-seven years, now under my care for a retarded depression, had grown very rapidly while attending a preparatory school between the ages of fourteen and sixteen years. He had a subnormal temperature ( $97.5^{\circ}$  to  $98^{\circ}$ ) the greater part of the time a low blood-pressure and slow pulse (60). He was "cold all the time," and for the greater part of two years he had syncopal attacks on the slightest physical shock, and finally had attacks quite independent of any apparent cause except when required to stand to be measured for a suit of clothing. These syncopal attacks left him weak and trembling. He was six feet tall at sixteen years. Under the advice of his physical trainer at school he engaged less actively in exercise, lived more in the open and took extra bed rest. No further therapy was followed and he recovered from the condition, the last symptoms to disappear being a moderate degree of flat-foot and a permanent ache. It is interesting to note that instead of being concrete-minded and a poor student, as in many of this class, he was the delight of his tutors and easily won several scholarships.

imbalance by atrophy of the thyroid or excessive functioning of the adrenals, but often they do not do so until they have debauched many of the visceral organs in function or structure, or both. In the severe grades of this disorder something radically wrong is earlier recognized and succor follows more promptly if not less surely.

While in a single case one might preach a whole series of medical lessons of neglect in accurate diagnosis, once the disorder is diagnosed the therapy is not essentially simple—least of all is it to be met upon the basis of glandular therapy. While the latter helps, our method of administration is so crude that we must give the gland with caution. No glandular therapy at all is almost better unless due attention is paid to all the other principles of physio- and psycho-therapy. In point of fact there are those who despair of ever finding so beautiful a sinecure of gland feeding for endocrinic dysfunction as thyroid administration in cretinism, and have preferred to assist their patients back to health without such aid. While this view is obviously empiric and not scientific it has much to recommend it. Let us see what is really at fault in our specific problem; First of all there is an enduring low blood-pressure and diminished sympathetic tone in the autonomic system. The viscera drains the blood from the cerebral cortex and syncope develops. Usually the adrenals and thyroids come to the rescue and reestablish blood-pressure, and vasomotor and sympathetic tone are incompletely resumed to await the next calamitous period. As might be expected, all these individuals are underoxygenized. Their tissue metabolism is slow to build up and they are in a state of chronic organic fatigue requiring an enormous amount of sleep. Every case immediately improves with continuous outdoor living and long hours of sleep, but how are these principles to be made permanent in a changing organism during adolescence when the physical and mental equipment for life is to be met? Fortunately the imbalance is not stubborn of correction nor is the fixation once obtained needful of enduring care and attention. It would seem as though the system once having gained its imbalance fixated upon its normal adaptive routine and thereafter made the individuals aware of over-stepping the rules within healthful limits. The whole organism is trying its best to adjust to a plan of overgrowth for the time being. Different bodily functions seem to make an effort to catch up or compensate for the extra skeletal and muscular spurt. The sympathetic and vasomotor systems soon expand and take up their belated functions. One might term the state a form of irregular structural growth of the body, resulting in a disharmony of functioning on the part of the different systems. Three cases out of many that are fairly illustrative are here given:

CASE I.—A boy, now eighteen years old, came to me at the age of fourteen years with a record of poor schoolwork especially in all abstract studies; he was two years in arrears. He had fainting attacks at infrequent intervals when required to stand perfectly still. One of these occurred while being examined and was accompanied by profuse perspiration. He was nearly six feet in height, had low blood-pressure (92) and slow pulse (64). He possessed a childish type of physique—had soft muscles and a piping voice. His movements were slow and awkward. His development during adolescence followed the father's physical and mental history. He was decidedly lazy, sluggish and indifferent to any form of intensive effort. He fatigued easily and required an enormous amount of sleep (twelve hours). Bed-wetting was a permanent habit, and at the age of fourteen it still occurred once or twice a week. A concrete outdoor training was advised, with continued long hours of sleep and also special tutoring. After six months of such treatment the father reported the boy as physically well, and he is now making up his schoolwork, although by preference he prefers an industrial or business career to a professional one.

CASE II.—A young woman, aged twenty-nine years, who has a fairly normal personal and family history aside from a paternal uncle having a sort of "breakdown" in early life, which, judging from the description, may have been similar to our patient's disorder; he had a very large physique and was considerably over six feet tall. After he left indoor work and engaged in agricultural pursuits he enjoyed comparatively good health. Our patient was born at full term, was the first child, healthy and weighed about ten pounds. She is the largest in the family, although all the siblings, four in number, are large built. When about fourteen years of age she had sudden syncopal attacks which came on without cause except when she was required to stand quite still. Immediately following these attacks there would be loose evacuations from the bowels attended by colicky cramps in the abdomen. Soon after these digestive symptoms there would be a sense of fulness in the head and pressure in the ears. These syncopal attacks came on at the time of rapid growth, but were ascribed to indigestion and soon disappeared. The period developed normally at fourteen years. She attended to all her duties encountered in a small New England town and gained a good school education, being particularly proficient in mathematics. Her emotional life developed normally. She taught school for seven years and liked her work, but, as she said, it pulled her down physically and the summer vacations failed to fully restore her for the beginning work in the fall. She was at last obliged to give up teaching on this account and took up Y. W. C. A. work. However, even this type of indoor work proved too taxing, and the syncopal attacks again appeared but unaccompanied by the diges-

tive symptoms. The present attacks come on without warning. She feels a coldness in the epigastrium and a sense of giddiness, which produces fright if she is alone, and she seeks to go to someone. If this is not possible she walks rapidly about, when the syncopal feeling passes off and she begins to feel tired all over. She believes she might faint if she did not move rapidly, although this apparently has never occurred. The attacks always occur by day, usually when she has been sitting or standing for some time. Her verbatim account of one of these is as follows: "I was feeling quite well when I got up. About nine o'clock I went to class and noticed my right hand was cold, but paid no attention to it. A few hours later I went to interview a teacher and found her busy, so I stepped into a room nearby and sat there alone waiting. Suddenly I experienced this sense of coldness, and I got up and walked toward a girl. I was about to attract her attention when I gained control of myself, although I did not feel natural. I was trembling, which is the usual effect after such a spell. There is never any abdominal sensation or indigestion now as formerly."

Physical examination shows a large physique; she is six feet tall. Her pulse was 60 to 64, blood-pressure, 87. There was a dermatographism and rather markedly cyanosed hands. Otherwise the physical examination was negative. In the absence of the voice sign the character makeup and any mental stigma of epilepsy the condition was diagnosed as a pituitary dysfunction in which the muscle and skeletal growth apparently outran a proper nervous and circulatory development. There was a marked tendency to gastroptosis and flat-foot; the muscles were flabby and the bony frame was loosely put together. She was given postpituitary and thyroid, with the injunction that she live an outdoor life with long hours of sleep. Too short a period has elapsed to note the final outcome.

CASE III.—This is the case of a young woman, aged twenty-five years, who is nearly six feet in height, which she attained at an early age and whose description corresponds to the previous history as to low blood-pressure, slow pulse, etc. Her first syncopal attacks occurred during her thirteenth year, and were liable to occur on a sudden change of position, such as rising quickly from a chair or from a reclining position. When called on in school to recite or read from the blackboard on rising quickly a wave of darkness would come over her like a cloud before the eyes. It lasted less than a minute and seemed like a slight obstruction of the vision, accompanied by a pressure across the top of the head. There was no state of exhaustion following. During this time she had grown very rapidly and was chronically constipated. The syncopal attacks gradually disappeared after instituting a hygienic outdoor life in the country. Her tendency to such attacks has been overcome to

the extent that she can now engage in indoor work without mishap, and is now taking a course in nursing.

Hardly any material may be found in the literature bearing directly upon our subject. For instance in Stier's work on *Syncopal Attacks*<sup>3</sup> he believes that the faintings are preceded by psychical states as precipitants—obviously a view illy in accord with our subject, wherein psychical factors play little or no role. Timme's<sup>4</sup> study, however, is more pertinent. His case material largely came under his purview because of extreme fatigability in adolescence and persistent headache. He makes no mention of fainting attacks, but otherwise outlines fairly sharply the physical characteristics of our material. He especially stresses the rapid growth, slow sexual maturity, vagatonia and low blood-pressure. In the final stages of middle life he states that petit mal may occur. His therapeutic suggestions are embraced largely in glandular feeding, and he does not seem concerned about detailing the process of compensation which nature uses in restoring the balance.

**Summary.** There are a number of rapidly growing adolescents who have relatively benign fainting attacks which at first seemingly simulate larval forms of petit mal epilepsy. They are to be differentiated from this latter condition by the absence of the epileptic character and the general physical and mental stigma of the grave disorder. The syncopal states are but a part of the obscure clinical picture of dispituitarism, in which there appears to be an excessive functioning of the anterior lobes of the pituitary gland. Coincident with the fainting attacks may be low blood-pressure, slow pulse, vasomotor ataxia and a host of defective muscular and skeletal displacements. In the psychical sphere one may encounter not infrequently character delinquencies and slow mental development. The line of corrective treatment is physical plus the administration of specific glandular substance. Mild cases recover of their own accord by gradually restoring the glandular and physical balance, but they can be materially helped by proper direction and rest. Timme states that in many cases of dispituitarism such as outlined in my paper the pituitary gland itself compensates by making some bony erosions and thus enlarges the sella for the proper functioning of this gland, and that this fact can be demonstrated by the roentgen ray. In my own cases the roentgen-ray examinations were uncertain of exact determination of this fact.

From the evidence in this brief paper one gains the fact that even in the large group of essential epilepsies and the psychoneuroses in which endocrine dysfunctions are present one must not charge too surely the dysfunction as a real but only a contributing cause for

<sup>3</sup> Syncopal Attacks, Especially among Children, Deutsch. med. Wehnschr., April 8, 1920.

<sup>4</sup> A New Pluriglandular Compensatory Syndrome, Endocrinology, 1918, 2, 209.



the nervous disorder, for many other precipitants of the disease are surely in evidence which are much more nearly related to the psychic disorder than the circumstance of an endocrinic disturbance. By assuming this position our special glandular therapy will not be too heavily charged with remissness when its administration solely results in failure. No two disorders existent in the same individual are essentially in the relationship of cause and effect.

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## THE UREA CONCENTRATION TEST.

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THE object of this paper is to compare the merits of the urea concentration test with some of the more common tests for kidney function.

The relation of kidney pathology to hypertension has been an extremely interesting and perplexing problem, especially the degree of renal involvement generally found in cases of hypertension, just how much latitude is allowable to the term "essential hypertension" and whether or not cases of hypertension exist for any appreciable length of time without some demonstrable abnormality in kidney function. Consequently when the work was started, some sixteen months ago, I had in mind the establishment of a routine method, or methods, of examination which would throw some light on the above stated questions.

The number of cases has been limited and the methods of technic were changed frequently in the beginning, therefore the results obtained from the work have been rather disappointing. However, a preliminary report will be given.

I was especially interested in the article by MacLean and De Wesselow,<sup>1</sup> in which they discuss the effects of "war nephritis." They conclude that patients with defective kidneys are unable, after receiving a large dose of urea, to excrete urine with a very high concentration of urea. Further, that the degree of concentration seems to bear a direct relation to the degree of kidney involvement.

The details of the test are as follows:

The patient urinates and at once takes 15 gm. of urea dissolved in 100 cc of water. One hour after taking the urea the patient voids. Two hours after taking the urea the patient again voids. The percentage of urea is calculated in both specimens. If the percentage

<sup>1</sup> Quart. Jour. Med., July, 1919.

of urea exceeds 2 per cent the kidney may be considered as fairly efficient; if below 2 per cent, some disturbance is present and the lower the concentration the more serious the lesion. Cases with a concentration below 1 per cent are rare, but many cases show a concentration of only 1.5 per cent. Occasionally one encounters a case in which marked diuresis is occasioned by the administration of urea, especially if the patient has been imbibing large quantities of water. These cases, of course, can be controlled, and if care is exercised usually a satisfactory test can be obtained. Generally speaking, the second specimen should not exceed 150 cc.

Before discussing the results which we obtained it might be well to discuss, in brief, the ratio of the urea content of the urine to that of the blood after the administration of large quantities of urea. There is a fact, or rather hypothesis, which confronts us when kidney function is to be considered—namely, the fact that no direct inference can be drawn as to the total functional capacity of the kidneys by the rate of excretion of urinary constituents: that is, the same kidney under the same conditions may excrete at one time much and at another time little. It naturally follows that attempts to draw quantitative anatomical, or even functional inference, from the amount of any constituents excreted, promise little help.

There are two fundamentally conflicting views which, up to the present time, have furnished a foundation for most of our kidney-function tests. Schlayer emphasizes the essential inconstancy in the rate of work of the kidney, even under normal conditions. Ambard, on the other hand, believes that variations in the rate of excretion of urinary constituents, under any and all conditions, are in reality manifestations of the constancy of kidney action, since they are exactly accounted for by the alterations of the concentration of these constituents in the blood and in the urine and do not result from inconstancy in the rate of work of the kidney itself.

Materials used as test substances should be those not affected by extrarenal influences. It will be remembered that Schlayer did not fully emphasize the fact that chlorides are subject to extrarenal influences and that the estimation of sodium chloride in the urine does not necessarily throw any valuable light on the subject of kidney efficiency, because the amount of chlorides excreted may be influenced by the amount of chlorides and water brought to the kidneys for excretion as well as by any degree of difference in the excretability of renal cells. The ideal test substance, therefore, would be a urinary constituent which is a true end-product, in that it is incapable of chemical alteration within the body and is one whose only path of excretion is through the kidneys. Urea fills these requirements to a considerable degree.

Addis has shown that the ratio between the urea content of the urine and that of the blood, over periods of twenty-four hours, is constant in normal individuals who have the same blood-urea con-

centration, while variations in kidney function arise from difference either in environment or in anatomical structure.

Ratios measured over short periods of time vary widely, even though the blood concentration be the same. Probably this variability is due to short-lived alterations in environment which counterbalance one another over a twenty-four-hour period of time, but not over one- or two-hour intervals.

In the normal individual, on a mixed diet, the blood contains from 12 to 18 mg. of urea per 100 cc. When renal function begins to fail, a point is reached at which it becomes difficult for the kidney to deal with the urea and other waste nitrogenous products, with the result that the concentration of these bodies increases in the blood. With an increase of urea in the blood the diseased kidney, of course, is able to excrete the normal amount of urea, and urea estimations alone may be misleading; thus it not infrequently happens that in a case of advanced Bright's disease we find that the average amount of urea excreted in twenty-four hours is equal to that excreted by a normal individual. It was supposed for a time that by estimating the urea content of the blood we could gain information that would throw much light on kidney function. However, it is not infrequent to find an individual with a high degree of kidney insufficiency carrying a normal blood urea content.

MacLean thought possibly we could determine whether cases with urea retention could be distinguished from those in which the blood urea was within normal limits by difference in the total amount of urea passed in a given time after a dose of 15 gm. of urea. This method failed entirely to differentiate between those patients in whom the blood urea was known to be above normal and those in whom no such retention existed. It was, however, noticed that the concentration of urea in the urine after the dose, appeared to bear a definite relationship to the severity of the case—that is, patients with urea retention passed relatively large quantities of urine with low urea concentration, while patients without retention passed smaller amounts with higher concentration.

As stated above we have not applied this test to a varied group of cases but purposely have confined our work principally to hypertension, and the results are given below.

I have chosen from the list only ambulatory patients who have a definite hypertension and whose blood-urea nitrogen does not exceed 20 mg. per 100 cc, the reason being that it is not our purpose to discuss, in this connection, cases of advanced Bright's disease.

There are fifteen cases in all. Seven pass more than 400 cc of urine at night. Three have a definite fixation of specific gravity over two-hour periods. Five pass less than 1 per cent sodium chloride in twenty-four hours. None has over 20 mg. urea nitrogen per 100 cc of blood. Seven excrete less than 50 per cent phenol-sulphonephthalein in two hours. Three concentrate 2 per cent or more urea in the urine following a dose of 15 gm. of urea.

No.	Age.	B. P.	Urine.	Mosenthal.	NaCl, per cent.	BUN: Blood urea:nitrogen	Phthalein.	Urea concentration test.
1	60	180-110	1.010-L. amb-acid-alb—few H. casts-480 NU	1.006-1.008	0.5	20	20-20-40	1.5 1.3 1.3
2	40	170-80	1.025-amb-alk-alb tr. few casts-340 NU	1.020-1.029	0.75	18	60-15-75	4.2 2.3 1.7
3	35	248-135	1.032-amb-acid-alb—Mic— 300 NU	1.025-1.032	1.00	15	40-30-70	1.4 1.7 1.9
4	50	170-95	1.021-amb-acid-alb—Mic— 400 NU	1.020-1.029	1.00	10	15-10-25	1.12 1.3 1.9
5	45	220-90	1.030-alb—mucus + few H. and FG casts 340 NU	1.012-1.034	1.00	15	25-30-55	2.3 2.15 2.67
6	41	220-130	1.022-acid-alb—Muc—Cyls + 250 NU	1.013-1.029	1.4	20	30-20-50	3.15 3.0 2.15
7	36	250-160	1.010(acid-alb tr. Mucus + Pus + 360 NU	1.010-1.014	0.5	15	5-10-15	1.7 1.27 1.27
8	60	280-180	1.012-L. amb-alb—Mic—460 NU	1.006-1.014	1.1	15	45-20-65	1.56 1.7 7.9
9	56	210-110	1.022-amb-acid-alb—few G. casts 390 NU	1.022-1.030	1.5	20	20-30-50	1.8 2.1 2.2
10	65	295-175	1.028-amb-acid-alb—few H. casts-450 NU	1.022-1.032	1.2	15	12.5-15-27.5	1.6 1.9 1.9
11	50	210-145	1.028-amb-acid-alb—few H. casts-450 NU	1.018-1.029	0.8	20	10-10-20	2.0 1.6 1.9
12	45	210-140	1.035-amb-acid-alb—few G. casts-Pus + 500 NU	1.030-1.041	1.1	10	30-15-45	1.4 1.3 1.2
13	37	210-100	1.031-amb-acid-alb—Mucus + Pus + 275 NU	1.026-1.032	1.2	15	30-25-55	1.6 1.98 1.2
14	37	180-60	1.018-amb-alb—Mis-Aortic Insuf.-380 NU	1.012-1.035	1.0	10	35-30-65	Wass 4 + + 4.0 4.0 + +
15	60	198-130	1.009-acid-alb—few H. casts- 230 NU	1.009-1.011	0.5	65	5-5-10	2.0 1.6 1.8

In the Mosenthal column, we have given the high and the low extreme in specific gravity.

In the phenolsulphonphthalein, we have given first hour, second hour, and total.

In the urea concentration test, the first figure represents percentage just before urea was given and the two following figures represent the first and second hours.

NU—Night urine.

CASE No. 15 is a bed patient, carrying a high concentration of blood-urea nitrogen, evidently a case of chronic interstitial nephritis. Case No. 14 has a positive Wassermann test and a definite aortic regurgitation. His function tests line up in a normal manner. These cases are given merely for comparison. (See Table.)

At first I was inclined to think that the urea concentration test offered little if any more than Mosenthal's two-hour test for specific gravity, considering as I did that both tests simply indicate examples of a common dysfunction—namely, the inability of chronically damaged kidneys to concentrate solids. But as the work advanced I became more and more convinced that this was not absolutely true. You will notice by the chart that only 3 of the cases had a low fixation of specific gravity and only 3 concentrate 2 per cent or more urea in the urine.

I think that the two-hour test for specific gravity gives us valuable aid in kidney function work, especially in the class of cases under consideration. It is extremely important to note the amount of night urine passed. Normally a kidney should be able to excrete the usual amount of nitrogen and other waste material in a normal amount of water; that is, 1200 to 1500 cc of urine should be passed in twenty-four hours with a specific gravity of 1.016 to 1.022. The night urine should not be more than 400 cc. However, with beginning Bright's disease usually one of the first complaints registered by the diseased kidney is for more water. It is unable to excrete the usual amount of solid material unless that material be diluted. The degree of dilution necessary usually runs hand-in-hand with the amount of kidney damage present.

It is of some importance when making these function tests not to change the routine diet or general living conditions of the patient, because we wish to determine the function of the kidney as it actually exists under the patient's usual mode of living and not what the kidney may be made to do under specific conditions. Therefore these patients were not put on any special diet, aside from our cautioning them not to drink water or other fluids between meals while making the two-hour specific gravity observation and also against drinking large quantities before the urea concentration test was done.

Relative to the solution of the questions referred to above—namely: the degree of renal involvement generally found in cases of hypertension, just how much latitude is allowable to the term "essential hypertension," and whether or not cases of hypertension exist over any appreciable length of time without some demonstrable abnormality in kidney function—I can give no definite answer, but I believe, basing my conclusions upon the Mosenthal two-hour test for specific gravity, the amount of night urine passed, and especially upon the urea-concentration test, that the longer the high blood-pressure exists the more kidney pathology one is

likely to encounter, and that the term "essential hypertension" should be limited to those cases in which every available function test has proved normal.

As to the urea concentration test I believe it possesses some merit. From the above observations, as shown in the table, it would seem that in high blood-pressure cases beginning kidney dysfunction may be noted at an earlier date with this test than with the function tests commonly used.

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**BILIARY TRACT DISEASE: SOME LESSONS LEARNED FROM  
DUODENOBILIARY DRAINAGE. FUTURE PROBLEMS.  
CITATION OF CASES.**

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*(Continued from January, 1922)*

*Comment.* This case illustrates biliary migraine in its purest form and the hope of relief which can be offered by this method of treatment. This case also illustrates how conditions of this sort, if unrecognized and untreated, inevitably lead later into the final states of gall-bladder pathology and calculus formation in the presence of a "masked" or unsuspected infection, especially when associated with catarrhal exfoliation. Even at this stage it could be repeatedly demonstrated that she was in the precalculus formation period by the finding of cholesterol crystals thrown out by a bile incapable of holding them in solution. We had in our series 19 cases which can be placed in this group. Only 1 other of these was in the pure form of biliary migraine represented in the case reported above. Seventeen had definite migraine sick headaches, with usually terminal biliary vomiting, but showed, in addition, different disturbances of function or pathological states of the biliary or gastro-intestinal tract. Of these, as a result of treatment, 13 showed complete arrest of the migraine, 3 partial arrest, that is, a lessening in the intensity and frequency of the attack, and 1 case made absolutely no improvement in this particular, although improved otherwise. In addition, 9 other patients exhibited severe headaches but not of the migraine cyclic type, and all 9 of them showed complete arrest of this complaint as a result of treatment. It has appeared to us that this group associated with headaches, biliousness and "masked" infection are in earlier stages of gall-tract

disease and often amenable to this form of treatment. Conversely we have frequently noted that in the group whose diagnoses of biliary disease can be made quite clearly on analysis of history and physical findings *alone* the patient gave us histories of having these severe migraine or migranoid headaches one to ten years previously, but are no longer complaining of them in their present account of their illness. Apparently, then, when they have passed through this phase spontaneously they are in a later stage of gall-tract pathology.

Mr. J. D. E., aged forty-two years, was referred to us on April 10, 1920. For eight years he has had recurring attacks of pain or distress and a sense of gnawing and weight-discomfort in the epigastrium, and bloating with belching. The pain was referred to the back when severe and occurred one to three hours p. c., and was relieved by eating or vomiting. The attacks were always in the spring of the year.

*Examination.* Asthenic. Pulse, 72. Two dead molars. Gums clean. Tongue clean. Tonsils red and retracted. Heart muscle was weak. The abdomen showed no rigidity but tenderness on deep pressure over the gall-bladder point and pressure over McBurney's point elicited pain referred to the epigastrium. "Tuning-fork auscultation" suggested adhesions of the stomach to the gall-bladder region. Spinal tenderness, 3d to 6th thoracic and 10th thoracic to the left. Hemoglobin, 90 per cent. Technical findings: Marked catarrhal duodenitis; catarrhal exfoliative cholecystitis with stasis and atony. Green-black "B" bile and pure culture, recovery of *Streptococcus hemolyticus*. Upon removal of tonsils the culture recovered only the *Streptococcus hemolyticus*. Vaccines of both were prepared and have been used alternately, with weekly drainage of gall-bladder. The gall-bladder atony has cleared up and general systemic improvement has followed. Streptococci are no longer recoverable from the bile by culture nor found in fresh or stained spreads, and the other abnormal findings in his bile have entirely disappeared.

*Comment.* This case suggested ulcer, based on the history, but biliary drainage proved the gall-bladder to be the seat of trouble, associated with duodenitis, and the subsequent response to treatment confirmed the diagnosis of "masked" infection of the gall-bladder with complete arrest of presenting symptoms, and final inability to recover the pathogenic infecting organisms on repeated culturation.

This case also illustrates the primary focus of infection in the tonsils transplanted to the gall-bladder, producing a secondary focus. It would therefore be fallacious to attempt to limit the treatment to the removal of the latter focus if the primary source of infection is ignored, unsearched for, and if found allowed to remain.

Dr. H. F. E., aged thirty-nine years, to whom we are indebted for giving us the following account of his personal experience with non-surgical biliary drainage in the treatment of acute cholecystitis complicating typhoid fever.

He was taken sick in April, 1920, with walking typhoid, during which period blood cultures were negative. He collapsed after the third week and was taken to a hospital, where he ran a typhoid course for ten weeks. He suffered a relapse after the fourth week. For three or four days previous to this relapse he had had considerable gas after meals and abdominal distention which previously had been relieved by enema. Enemas no longer removed the gas and suddenly one evening the patient was taken with acute distention in the region of the gall-bladder, at the left edge of the right hypochondrium, preceded at seven in the evening with a slight chill. There was no appreciable rise in the leukocytes. Gradually the pain became so severe that at 1 A.M.  $\frac{1}{6}$  grain of morphine was given, followed by  $\frac{1}{4}$  grain, without relief. The pain increased and another  $\frac{1}{4}$  grain was given. The pain became so excruciating that the patient screamed loudly and begged to be put under anesthesia. Dr. Doyle was called and washed his stomach, with no relief. A duodenal tube was then passed. No relief was experienced when the tube entered the duodenum, but instant relief came within five to ten minutes after magnesium sulphate was introduced and bile began to flow. In half an hour he was perfectly comfortable. From a subnormal temperature before his attack the temperature rose abruptly during the attack to  $106\frac{2}{3}^{\circ}$  F. and dropped again to  $100^{\circ}$  F. immediately after biliary drainage was established. Dr. E. went to sleep with the tube in place within half an hour. The tube remained in the duodenum overnight. The bile was very dark, very tenacious, cloudy and was a deep green-black. The next day he was fairly comfortable and the tube was kept in until 8 or 9 A.M. About 18 ounces of mixed bile was recovered during the night. The tube was inserted again in the evening without washing the stomach. Bile flowed immediately after introduction of magnesium sulphate, but was not so dark. The bile was at first viscid but became progressively thinner and lighter in color as the drainage was repeated daily for four or five days, then every other day. The bile always gave positive cultures for typhoid bacilli, even up to Dr. E.'s discharge from the hospital, about six weeks later. The total number of drainages given in the hospital was about twenty-two. He went to Atlantic City immediately after his discharge, where his nurse gave him a drainage treatment two or three times a week for three weeks. Thereafter during that summer, in the White Mountains, he gave himself a treatment on three occasions. No final cultures were made from his bile. He has remained well for eight months, has been in active practice and says he feels perfectly well.

His history previous to typhoid fever was briefly as follows: He



had had no infections, except that in Pittsburgh, in 1912, when he was a hospital resident, he had two gall-bladder attacks preceded by conjunctival jaundice. Roentgen-ray examination was negative. He was in bed for ten days each time. Between 1903 and 1907 he had recurrent attacks of follicular tonsillitis, but the tonsils were not removed.

*Comment.* This is a most important type of case in which this method of treatment has great promise. We all know how serious operative interference may be for acute conditions arising as complications during the acute and prostrating infectious diseases. Surgery has successfully managed some of these cases but the mortality has been high. But surgery, until recently, has been the sole choice and the risk taken was warrantable. Now we have a alternative choice, which can be more safely tried, and, if successful, the operative risk is avoided.

Secondly, this case teaches the lesson of the importance of the detection and treatment of typhoid carriers, as commented on in a previous paper.<sup>8</sup> This has been emphasized, too, by Nichols and others<sup>2</sup> and later by Henes.<sup>10</sup> Dr. E. is not yet safely out of the woods and should be reexamined for residual infection both for the sake of himself and of others.

Third, this case is similar in its acute picture to 2 cases, within the past two years, of acute empyema of the gall-bladder which were successfully treated by this method: One in a man who, for business reasons, positively refused the operative course advised him and the other in a woman who had such a severe cardio-renal disease as to imperatively contraindicate surgery if there was any other acceptable alternative.

If the gall tract in any given case can be made to successfully drain by this method the patient may be safely tided over the acute phases. If it cannot be successfully drained, surgery become imperative. Naturally this method should not be advocated if there are no surgical contraindications, since otherwise surgery becomes the absolute choice of procedure providing *safe* surgical skill is available.

Mrs. R., aged thirty-three years, referred to us on August 6, 1920, was operated upon eight years ago for empyema of the gall-bladder. A cholecystostomy was done but a biliary fistula developed through which she was drained constantly for *eight years*, with the exception of several weeks, when the sinus remained closed following cauterization. She has worn a dressing pad constantly, and during this period has not remained pain free for longer than a month, and usually has had recurrent attacks of the upper right quadrant pain referred around the costal margin to the right shoulder-blade every four to twelve days. Five years ago, for the relief of pain, she began to use a small silver catheter, which was introduced into her

gall-bladder every night and morning by her husband, who had become most expert with it. It was noticed that she was more liable to be pain-free when bile was recovered by the catheter, but when thick white mucus and no bile was aspirated a pain attack very quickly followed. This suggested that the cystic duct became blocked by mucus secreted by the racemose glands at the neck of the gall-bladder and a hydrops of the gall-bladder would probably have followed if this mucus could not find an exit by way of the fistula. During these pain attacks there was frequently associated chills and fever for a day or two, with stiffening of the upper right rectus. Another surgeon (who referred the case to us) had watched the patient through many such attacks for three years and had made several attempts to close the sinus tract by cauterization, but with no permanent success.

When she first presented at our office we catheterized the gall-bladder, and by means of a small syringe obtained a greenish-brown bile (with much mucopus flocculations in it) for culture and cytological examinations. The latter showed most beautifully the type of tall columnar bile-stained epithelium which we had previously seen in many other cases, and had, we think, learned to correctly classify as gall-bladder epithelium on account of its height and its tendency to break off from the basement membrane at the reticulated folds of the rugæ and to become arranged in fan-shaped masses. With this epithelium was found much inflammatory débris, pus cells and many colonies of heavily bile-stained bacteria. The following day we checked up our findings by duodenobiliary drainage and recovered the *same type bile*, with the *same cytological picture* of the mucopus floccules, and Dr. Richardson recovered from our cultures from both sources the *same bacteria* (and only them), namely, a hemolytic streptococcus and the *Bacillus coli communis*.

A gall-tract drainage was given every fifth day and each one was followed by an attack of upper right quadrant pain. This we have noted very frequently in our series of the more acute cases of gall-bladder inflammation and perhaps more frequently with those infected with streptococci. This seems a natural result of making the inflamed viscus empty itself, but in all of our cases, except one thus far, the pain following such drainage has become less severe until none is felt. After the third drainage and injection of vaccine, the sinus closed and *has remained closed since* (now eight months) but two days later an acute attack of pain occurred, with moderate fever, chills and leukocytosis and a surgical type of the upper right quadrant. There were no untoward developments after one week's hospital observation, and treatment was then resumed on the following basis: A duodenobiliary drainage daily for three days, then twice a week for four weeks, every seven to ten days for another month and thereafter every three weeks. An autogenous vaccine

was made and administered every fifth day, and at first gave rise to a definite focalizing gall-bladder pain, and after four months the streptococcus disappeared from our cultures and since then on seven cultures made every third week only the *Bacillus coli* has been recovered. We have seen this disappearance of streptococci following autogenous vaccination and drainage in twelve cases of our series. Her pain attacks persisted after each drainage for the first month, but for the past seven months she has had none. Not only has she had a complete arrest of symptoms, but there has been a general systemic improvement in endurance, in color, in bowel function, appetite, sleep and general sense of well-being. In addition, and this is the important point which we wish to stress, there has been a steady though gradual disappearance of all the abnormal cytological findings from her bile. Her gall-bladder drains readily in response to magnesium sulphate and apparently continues to function normally between treatments, and we believe now that her focus of infection has been permanently eradicated. She sailed for Italy last month, taking with her a duodenobiliary drainage outfit, and will continue to give herself a treatment (as many patients have been taught to do) once a month. They find it very easy to do. We believe it to be a good prophylactic policy for them to follow and will guard against relapses.

*Comment.* We have recited this case in some detail because it has been one of great interest and instruction to us: First, because we were able to obtain bile by direct catheterization from the gall-bladder for microscopic examination and culturation, and, secondly, because of our recovery by the duodenal route of the same type bile with identical cytology and bacteriology we have again satisfied ourselves that this method of diagnosis and treatment (as one of us has previously presented it) is fundamentally correct, and is, moreover, a practical and efficient procedure; and, third, that a bacterium thus isolated in pure culture, and given as a vaccine, has a definite and specific therapeutic value in closing a sinus and overcoming a focus of infection in the gall tract; and, finally, that the possibility of the specificity of the bacterium is enhanced if it gives rise to a focalizing reaction which reproduces one or more of the presenting symptoms.

During the past year we have closed successfully by this method one other case of persistent biliary fistula of months' duration, this second case being infected with *Staphylococcus aureus* and *Bacillus coli*.

Mr. M. R. E., aged twenty-nine years was referred to us on August 5, 1920. He presented historically a mixed syndrome of a gnawing pain-distress in the epigastrium, occurring two or three hours after meals, relieved by eating or alkalis, but followed by post meal-belching and upper abdominal distress. These symptoms first

appeared about one year ago and have been featured by their intermittent appearance and spontaneous total remission.

His past history brought out the following important points: He was a "blue baby" for several months, but apparently recovered without serious damage to his heart. He had been subject to recurrent attacks of tonsillitis every winter for several years. In 1918 he had a severe attack of pandemic influenza, with chiefly intestinal focalization. In 1902 and again in 1906 he had suffered attacks of typhoid fever, both apparently genuine, but not accompanied by relapse or complication. Furthermore, his story suggested there was a possible typhoid carrier in his family, inasmuch as he said that his mother had had typhoid fever three times, and one brother and sister each had had one attack. He, himself, had been subject to bronchitis for years.

On physical examination the positive findings were as follows: Two dead and many decayed teeth requiring fillings, but no root abscesses. His tonsils were badly diseased and infected. He had chronic bronchitis with musical dry rales. There was slight rigidity of the upper right rectus, but no tenderness. The gall-bladder was not palpable. By "tuning-fork auscultation" there was definite transmission of the gastric note to the left edge of the right costal margin, but not transmitted through the liver. This we have learned to interpret as being very suggestive of adhesions between the pylorus or duodenum and the gall-bladder. When the gastric note is clearly transmitted through the liver the adhesions are more liable to be denser and attached to the under surface of the liver itself.

As a result of technical examination we found that Mr. E.'s stomach had escaped organic damage, but showed a fractional curve of hyperchlorhydria, with the suggestive extragastric terminal elevation. He gave evidence of an exfoliative duodenitis and a catarrhal and infected cholecystodochitis, with pericholecystic adhesions obstructing the cystic duct. Cultures from this bile recovered a hemolytic streptococcus and *Bacillus coli*. The roentgen-ray study of his gastro-intestinal tract was reported summarized as follows: "Duodenal ulcer with periduodenal adhesions. The gall-bladder is not visualized." We, however, were unable to develop clinical or laboratory evidence to support this diagnosis of duodenal ulcer and felt that we had to deal primarily with an infected gall tract with periduodenal-cholecystic adhesions.

As a preliminary plan of treatment following our usual custom he was referred for the necessary dental work, and his tonsils were taken out, 50 per cent of the crypts were cultured, and a pure culture of hemolytic streptococci, like that isolated from his bile, was recovered and the two were mixed and used as a vaccine.

After several therapeutic duodenobiliary drainages had been given him we noted the fact that only one out of five recovered "B" or

gall-bladder bile, and increased our conviction that the cystic duct was obstructed and, although he had made some improvement, we referred him for operation. At operation our diagnostic conception of the case was verified. He was found to have no evidence of duodenal ulcer, but running from the lateral and anterior surface of the second portion of the duodenum to the mid-region, and to the neck of the gall-bladder were fine bands of adhesions which angulated the gall-bladder at two points. The gall-bladder was long and distended and could not be emptied by digital pressure. The gall-bladder was opened and a culture taken from which the hemolytic streptococcus was alone recovered. The mucosa was reddened and granular but not of the strawberry type. The cystic duct was probed and found obstructed just below the neck of the gall-bladder at a point where the adhesions were attached. In freeing the adhesions the gall-bladder was so badly traumatized that it seemed wise to remove it. The patient made a good postoperative recovery for two months, but then partially relapsed, and, on reculturing his bile, the *Streptococcus hemolyticus* was again recovered, together with *Bacillus coli*, and the duct bile microscopically still showed the inflammatory findings of a residual duct infection. Postoperative duodenobiliary drainage was then instituted at weekly intervals and the new vaccine administered with prompt symptomatic response, and at the end of ten treatments the streptococcus disappeared from the cultures, and a month later the bile was reported sterile and has remained so since. The positive cytological picture of residual duct catarrh also cleared up by degrees and is now normal, although he has had no treatment for two months, and the patient is perfectly well and fifteen pounds heavier. It is interesting to note that the typhoid bacillus was not recovered from his bile by tube drainage or at operation.

*Comment.* This case again illustrates the importance of realizing that the so-called duodenal ulcer syndrome, based largely upon the history when unsupported by other clinical or laboratory data, bears an unreliable reputation and will trap the unwary or careless diagnostician. We must learn that the one- to three-hour postmeal epigastric empty distress, or so-called hunger pain, does not necessarily mean ulcer even when the pain is relieved by eating or the use of alkalies or antispasmodics, but should rather be thought of as a *mixed syndrome* in which duodenal irritation short of ulcer, with or without adhesions, cholecystitis and appendicitis, or combinations of them, must be differentially proved. Rarely, as Eusterman points out,\* benign gastric tumors may simulate the so-called duodenal ulcer syndrome.

The second diagnostic lesson this case teaches is that the roentgen-ray diagnosis of duodenal ulcer cannot always be separated clearly

\* Dr. Eusterman's paper has not yet been published.

from duodenal adhesions and that the final diagnosis should be made by adjusting a proper balance between the history, physical findings and the data obtained from laboratory studies.

The third diagnostic lesson taught us by this and other cases is that when we fail to recover "B" or gall-bladder bile after several attempted drainages it is strong evidence in favor of an obstructed cystic duct or a fibrous, atrophic functionless gall-bladder or one filled with stones and containing no bile. This is diagnostic evidence of great value to the surgeon when preoperatively secured.

The therapeutic lessons we learned from this case and others similar to it are:

First. That the great primary essential in the treatment of these cases, whether medically or surgically managed, is to first remove all foci of infection higher up which may have caused (or may retard the healing of) the lesion in the upper right quadrant.

Second. That this method of non-surgical biliary drainage is not therapeutically applicable to *gall-bladder* disease in which the cystic duct is obstructed in such a way that the gall-bladder is unable to discharge its fluid contents.

Third. That this method of non-surgical biliary drainage has a very large and important field of usefulness in postoperatively continuing the surgical principles of free drainage in such cases in which surgery alone has failed to eradicate all residual infection. Duodenobiliary drainage, together with the use of autogenous vaccines, will prevent many of these cases from relapsing and will relieve both the surgeon and the patient from the vexatious and dangerous necessity of reoperation.

Mrs. E. R., aged forty years, was referred to us on August 19, 1920.

*Chief Complaint.* Pain in the right upper abdomen radiating to the back.

*Family History.* Father dead; renal, aged fiftythree; mother dead, cancer of breast, aged fifty-six years.

*Present Illness.* Attacks of acute epigastric pains, stabbing and grinding for six years; vomiting of undigested food two or three times a week, but during the past six months the picture changed and she had had about once a month severe attacks of nocturnal colicky pain in the right hypochondrium, radiating around the right costal margin. No jaundice but sallowness at times. Frontal headache and at times occipital. Eggs and beef disagreed. She became easily tired and was drowsy most of the time. There was epigastric bloating relieved by belching and epigastric pressure gave slight relief. The pain is generally nocturnal and unrelieved by food-taking. Vomiting of food as eaten, with bile and mucus. Constipation was obstinate. Mouth negative, except coated tongue. The abdomen was diffusely tender at McBurney's point and under the right costal margin, but the gall-bladder was not palpable.

In two attempted successive biliary drainages the gall-bladder failed to drain at first, and in the second only 32 cc of dark green turbid bile were recovered. At the same time the patient had an attack of pain similar to the previous attacks. Many cholesterol crystals were found in the bile and much amorphous bile salts. Culture: *Bacillus coli* (heavy growth).

Urine: Negative; 90 per cent elimination of phthalein in three hours (80 per cent in two hours). Blood: Hemoglobin, 85 per cent; white blood count, 7100.

*Comment.* An operative decision was made for this patient on the following grounds: She presented a clear-cut picture of gall-stone colic with increasingly frequent attacks. Her diagnostic drainage suggested a partially obstructed cystic duct and showed an infected bile microscopically suggestive of cholelithiasis. We believe all definitely proved gall-stone cases with *irritable* gall-bladders and infection should be operated upon unless there are operative contraindications present which may jeopardize the life of the patient. We are still in doubt as to the wisdom of routinely insisting that definitely proved gall-stones, when quiescent and with no history of previous activity, is, *per se*, an operative necessity. We believe there is no cure for gall-stones except the knife when skilfully used, and that the presence of calculi increases the likelihood of cancer of the gall-bladder. We believe that gall-stones in the presence of active infection make the gall-bladder more irritable and increase the tendency to colic attacks and to traumatization of gall-bladder tissue which may accelerate cancerous growth. Therefore such cases more imperatively require operation. But we further believe that preoperative diagnostic drainage will be of great service to the surgeon in suggesting what may be found at operation; that the fact that obstruction of the cystic duct preoperatively ascertained will be advantageous to know; that the determination preoperatively of the presence and the nature of the infection by cultural identification (to be checked up during operation) will be information of great importance to the surgeon in guiding him in what operative procedure to adopt, and especially will this be true if the preoperative study suggests the presence of duct infection in addition to bladder infection, calculous formation or obstruction of the cystic duct.

We are especially gratified to see the publication of an article by a surgeon (Dr. Whipple<sup>15</sup>) endorsing these views.

Finally, we believe that no case falling in this group should fail to have a postoperative study within two months after operation, and if catarrh or infection is still demonstrable duodenobiliary drainages should be instituted and continued until normal findings are secured. Indeed, prophylactic drainage might well be given once each month to forestall a relapse even in a surgical case apparently cured. It is true that in a number of instances we have

recovered very small stones through the tube and larger stones from the sieved stool following a diagnostic drainage; but there are doubtless others left behind, especially so if faceted stones are recovered; yet we do not advocate this method in the treatment of cholelithiasis, because we see the possible danger of perforating a cystic or common duct with a stone impacted in it.

To continue: Operation on this patient early in September, 1920, disclosed a gall-bladder containing thirty-two stones, brown, hard, faceted, pea to marble size. One stone in the cystic duct partially occluded it. A cholecystostomy only was done. Culture at operation, direct from the gall-bladder, recovered *Bacillus coli* only.

Postoperative study, ten weeks after operation: Gall-bladder drainage gave 50 cc golden-brown, viscid bile, flowing intermittently. Microscopically: Cholesterin crystals and some amorphous salts. Culture: *Bacillus coli*.

*Further Comment.* We are presenting this case to illustrate the points that symptomatic relief is not always a cure. The removal of the stones gave symptomatic relief, but the subsequent finding of the same organism, and the same inability of the bile to hold its salts in solution, is far from a cure of the condition. All the factors that are theoretically necessary for the production of stones are still present, and there is no assurance that they will not reform. In this group of cases postoperative biliary drainage by this method, from time to time, has served to clear up the remaining evidence of disturbed physiological chemistry and bacteriology in a number of cases.

Mr. M. H. A., aged twenty-five years, was referred to us on October 25, 1920. He is by occupation a draughtsman, and his most important personal complaint was that he was afraid he would lose his position because of an overpowering drowsiness that made him fall asleep at his work. His drowsiness was so great that he could not stay awake during the most exciting play or "moving picture." With this drowsiness was a progressive sense of fatigue, noticed during the past year, and a gradual loss of mental keenness during the preceding five years. Prior to this he had considered himself in robust health until he first began to notice dizziness and mental hebetude. In March, 1917, and again a year later, he had attacks of jaundice, with no other symptom except loss of appetite: furred tongue, headache, drowsiness and constipation. Both of these attacks suggested at the time a simple catarrhal jaundice, and the cloudy urine and light colored stools cleared up in several weeks, yet he continued to have dizziness, increasing drowsiness, increasing fatigue, cloudy urine after excess of sweets and bimonthly attacks of frontal headaches and more or less slight jaundice of the sclerae. About a year ago he became more positively jaundiced, with cloudy,



reddish-brown urine, but no noticeable absence of bile in his stools. During this year he says he has grown very melancholic and pessimistic, although he has nothing to account for it. He has lost twelve pounds during the past year and now weighs 158 pounds.

Except for belching immediately after meals and avoidance of sweets, onions and coffee he had no gastro-intestinal complaints. Other than recited he had had no previous infection except recurrent tonsillitis during childhood, for which his tonsils were removed when he was seven. From the ages of fifteen to nineteen he had *acne vulgaris* very badly.

The salient points in his physical findings were as follows: Large frame, good musculature. The face is broad, forehead narrow and low and heavy lower jaw somewhat of the acromegalic type. The lids are puffed, the hair grows low on forehead and temples and is thick and stiff. The fingers are slender, however, with thumb moons only. The skin is quite markedly jaundiced and shows *acne pustules* and old scars. The scleræ and roof of the mouth are also jaundiced. Hypertrophic rhinitis and catarrhal pharyngitis. Tonsils are out and tonsillar fossæ are clean. Tongue slightly coated but firm. Gums clean. Teeth regular except one non-erupted wisdom. Posterior cervical and left epitrochlear glands are palpable. Reflexes normal. Lungs and heart normal.

*Abdomen.* Distinct upper abdominal fulness. No tenderness, muscle rigidity or spasm. Liver enlarged downward, the hard, rounded edge being palpable to 10 cm. below the costal margin. The spleen is greatly enlarged and hard and extends into the left abdomen to the navel. The edge is rounded rather than sharp. Splenic dulness is enlarged in its percussion area well back into the left flank.

Technical Examination: Blood Wassermann negative. Hemoglobin, 93 per cent; red blood cells, 4,740,000; white blood cells, 9500.

• Polymorphonuclears, 65 per cent; lymphocytes, 25 per cent; large mononuclears and transitionals, 6 per cent; basophils, 3 per cent; eosinophils, 1 per cent. There was no change in shape of the red blood cells, but a noticeable microcytosis (common in hemolytic jaundice—Crawford). There was also an increase in skeined or reticulated red cells to 3 or 4 per cent. Coagulation time, five and a half minutes (slide and horsehair). A fragility test of his blood by Dr. E. B. Krumbhaar showed complete hemolysis up to 0.40 per cent NaCl, and partial hemolysis up to 0.60 per cent NaCl. This is a distinct lessening of both maximal and minimal resistance and points to a hemolytic factor in the production of his jaundice. This type of jaundice was also suggested in the absence of bile findings in his *urine* and its presence in the *stools*, both of which were otherwise negative.

*Stomach.* The fractional curve was one of hyperacidity, reaching its maximum of 110 total acidity and 80 free HCl at from seventy-five to one hundred and five minutes. No occult blood. Slight biliary regurgitation at seventy-five minutes. Normal amount of mucus. Motility normal. Fasting residuum: Study suggested an infective exfoliative gastritis.

*Duodenal Examination.* Disclosed an infective exfoliative duodenitis.

*Biliary Drainage.* When we came to an observation of his biliary drainage we encountered a type of "B" and "C" biles that we have never seen before in over 4000 examinations. The common duct was closed but opened promptly in response to magnesium sulphate. The "A" bile was a brownish-red, turbid, with increased mucus and viscosity. The transition to "B" bile was very prompt and the gall-bladder appeared to be under tension and discharged 320 cc of a greasy, thickish, paint-like bile of a deep reddish-brown color, turbid and containing many mucopus flocculations. It was delivered with a steady flow as though under pressure. Toward the end of the drainage there could be seen through the glass window in the tube *two* currents of bile, the most dependent one of heavier gall-bladder bile being of the color and consistency of red-brown paint and the upper current a transparent thinner bile, almost Burgundy red in color, similar to but darker than a hemolyzed blood Wassermann tube. This was the "C" or liver bile and also flowed rapidly. Over twelve ounces were recovered in less than an hour.

The microscopical examination of the mucopus floccules from the "B" bile showed many bile-stained oval and cuboidal cells in masses and strands and appearing to have a tubular architecture. Occasional masses of heavily bile-stained tall columnar epithelium were seen. The whole microscopic field was swarming with bacteria in masses and colony formation and the bacteria seemed to be entirely cocci. Culture from this bile gave a pure recovery of a *very* hemolytic streptococcus from which a vaccine was prepared.

*Comment.* This case was classified as a hemolytic jaundice with splenomegaly, catarrhal infective cholecystodochitis and biliary cirrhosis. After eleven drainages he had made remarkable progress, with a marked subsidence of his presenting symptoms. He was markedly improved in his mental state and in endurance, was keen and alert and no longer falling asleep at his work, and the jaundice was very much lessened. His liver had decreased in size so that its edge was just palpable at the costal margin and, to our surprise, his spleen was so much smaller as to be difficult of demonstration.

Dr. Krumbhaar had told us that in his opinion this was the type of case for which no medical plan of treatment had in the past proved effective and for whom a splenectomy offered the only hope. He urged our persistence in the plan of non-surgical drainage and

use of vaccines to see what might be accomplished. Up to date this man has been given about twenty-five drainages with *progressive improvement*. His skin is no longer jaundiced and there is only a subicteroidal tinging of scleræ and roof of the mouth. His biles are nearly normal in their gross appearance and the cytological picture is much improved. The liver is again of normal size, and although the splenic area to percussion is still enlarged the spleen itself is no longer palpable within the abdomen.

We are extremely interested in the outcome of this case. If the clinical improvement so far secured can be increased or made permanent over an extent of one or two years it will open up an enlarged field of usefulness of this method. While we are at present engaged upon some physiological and chemical studies on this patient a great deal of further work must be carried through before we can understand thoroughly the underlying factors concerned in producing this condition. We believe that continual duodenobiliary drainage day and night, over a period of two or three weeks, with an interruption of a like period, (after our manner of treating chronic arthritis)<sup>12</sup> might accomplish a prompter and more conspicuous improvement. This plan was suggested to this patient, but declined on the grounds that he was feeling so well that he did not feel justified in absenting himself from his work.

This is one of the problem diseases of internal medicine that may be in the future succesfully combated by this method. Pernicious anemia, Banti's disease, biliary cirrhosis, toxic cholecystodochitis and hepatitis may be benefited by this plan. Diabetes has already been treated with some success.

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## THE DIAGNOSIS OF PERITONITIS AND PERITONEAL TRANSUDATES IN INFANTS BY MEANS OF ABDOMINAL PUNCTURE WITH THE CAPILLARY TUBE.

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IN a preliminary communication a method was demonstrated which had been used in the diagnosis of a few cases of peritonitis and peritoneal effusion.<sup>1</sup> Since then the technic has been modified and the method has passed the experimental stage.

The original procedure consists in puncturing the skin with a metal needle, and through the opening thus made, inserting into the peritoneal cavity a glass needle with a capillary bore. Fluid rises in the glass tubing by the force of capillarity. In order to obtain larger amounts the tube was bent and a bulb was blown for the collection of the fluid. The objections to using glass needles are obvious, and the only advantage that still remains over the modification to be described is that a larger amount of fluid may be collected in the bulb of the glass needle. This advantage is insignificant compared with the greater safety in the use of the metal cannula, trocar and capillary tubing.

Only the latest, and thus far the most satisfactory, instrument, will be described.<sup>2</sup> It consists of a trocar-cannula and glass capillary tubing, and is shown in diagram in Figs. 1 and 2. The cannula is held by a handle and the shoulder is as short as it can be made. The shaft of the cannula is 17 gauge and  $\frac{1}{2}$  inch in length. It has a sharp beveled point, and the trocar is made to correspond.<sup>3</sup>

Most of the capillary tubes were prepared by the author from glass tubing 4 mm. in diameter. This tubing was drawn out in the Bunsen flame and varied in thickness. Only those parts were used that fitted the shoulder, or rather the proximal part, of the shaft, and the tubing was cut off so as to protrude 1 or 2 mm. from the end of the cannula. The purpose of this technic is to prevent breaking the capillary tube within the peritoneal cavity. The cannula with the capillary tube prepared in this way is illustrated diagrammatically in Fig. 3. The capillary tube impinges upon the wall of the cannula at *A*. After the tubing is safely inserted into the cannula as far as it will go a break, if it occurs at all, will take

<sup>1</sup> Denzer, B. S.: *Am. Jour. Dis. Children*, August, 1920, 20, 113.

<sup>2</sup> The instrument was made by the Randall Faichney Company, of Boston, Mass.

<sup>3</sup> A cannula with a flat end and trocar with an arrow-head point, similar to the larger instruments for abdominal paracentesis, was tried but was found unsatisfactory.

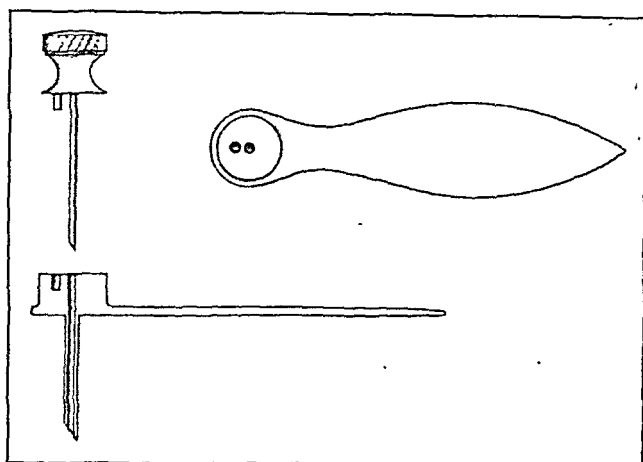


FIG. 1.—Trocar and cannula and top view of cannula. Semidiagrammatic cross-section.

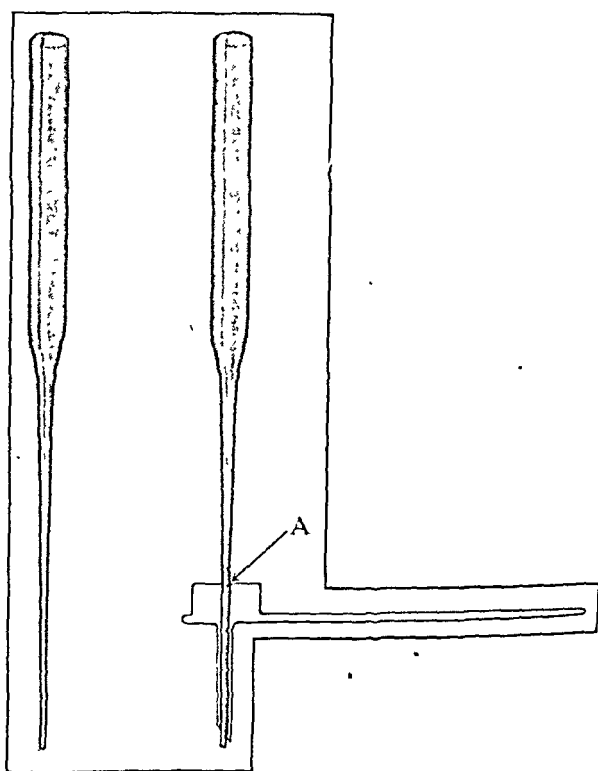


FIG. 2

FIG. 3

FIG. 2.—Capillary tube as prepared by author.

FIG. 3.—Cross-section of capillary tube fixed in cannula at A.

place above the point *A*, and the lower fragment, firmly fixed in the shaft, can be withdrawn with the cannula. Some of the capillary tubing was prepared by glass blowers (Fig. 4).

When glass tubing is used repeatedly the utmost precautions are necessary to obtain clean surfaces. As capillarity depends upon the capacity of the liquid to moisten the surface of the tube a minute film of fatty material might check the rising column of fluid. Cleaning fluid, hot water, alcohol and ether are used in obtaining clean glassware.

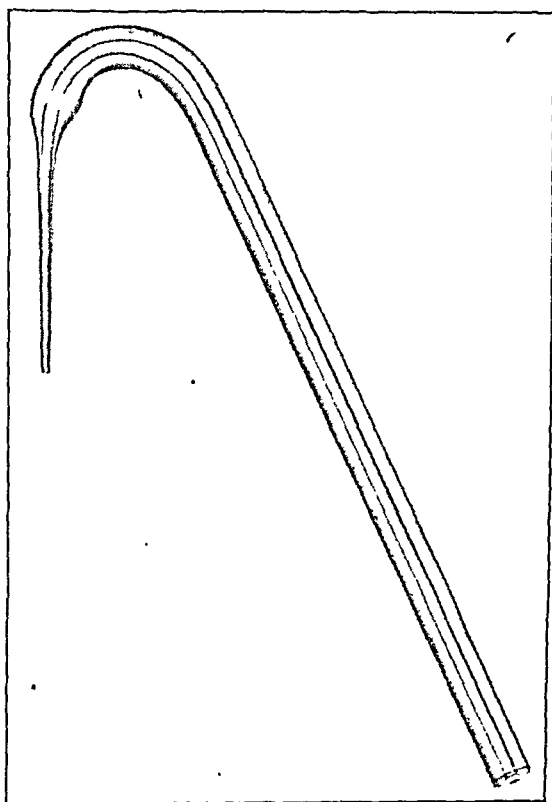


FIG. 4.—Capillary tube prepared by glass-blower.

The technic with the trocar-cannula and capillary tube is as follows: After sterilization of the skin and the usual precautions to determine bladder distention the point of the trocar-cannula is thrust through the skin and into the peritoneal cavity. The trocar is withdrawn and the capillary tube inserted as far as it will go. It is advisable to wait a few minutes and turn the needle in various directions before concluding that there is no fluid. Possibly a bit of omentum or the wall of the intestine may temporarily block the capillary tube; or when there is only a small amount of fluid this momentary wait and the straining and crying of the infant may distribute it over the entire peritoneal cavity. Any place on the abdomen except those parts covering a solid viscus may be used.

As a rule the midline just below the umbilicus is the site chosen, though punctures have been done in the iliac fossæ.

**Peritonitis.** The peculiar difficulties encountered in the diagnosis of peritonitis in infancy are too well recognized to demand lengthy discussion. Some of the classical signs and symptoms of peritonitis in adult life, such as pain, localized tenderness, distention and paralytic ileus, are either absent or difficult to elicit, and even when present they may be ascribed to minor gastro-intestinal disturbances, of which they are likewise characteristic signs. Standard textbooks on pediatrics and special studies on peritonitis in infancy<sup>4</sup> emphasize these difficulties. In 5 cases abdominal puncture with the capillary tube has been used in the diagnosis of peritonitis.

**CASE I.**—Edward T., a colored boy, aged three years, was admitted to the pediatric service of the New York Nursery and Child's Hospital on April 20, 1920. No history was obtainable. On admission the temperature was 103° and thereafter showed wide variations—from 2° to 6°. Chest signs and a positive von Pirquet pointed to pulmonary tuberculosis and the septic type of temperature suggested generalized tuberculous infection as well. On May 5, two weeks after admission, abdominal tenderness was first noted. The abdominal signs, though variable, became more and more definite, but the generalized tuberculosis rendered the diagnosis of acute peritonitis uncertain. On May 16 and 17 vomiting occurred, and on May 17 an abdominal puncture with the capillary tube was done. Whitish fluid rose in the tube and smears showed pus cells and Gram-positive cocci in chains. From a blood culture taken the same day a hemolytic streptococcus was grown. On May 18 a laparotomy was performed by Dr. Truesdale.

There was fluid pus in the peritoneal cavity; the appendix was swollen and red, but not ruptured. The child died the same day, and at autopsy generalized tuberculosis and purulent peritonitis were found.

**CASE II.**—Baby L., a colored infant, aged two months, weighing six pounds six ounces, was admitted to the hospital on July 19, 1920. As the baby was a foundling the history was incomplete. At the first examination, Dr. Anderson, the resident physician, made the following note: "The baby presented the usual picture of a true marantic—worn, anxious expression; thin, emaciated body; dry and inelastic skin." At first the baby's abdomen was distended, but during the twenty-four hours after admission it became distinctly softer. Marasmus, with the possibility of luetic infection, was the diagnosis considered.

<sup>4</sup> Abt, I. A.: New York Med. Jour., 1917, 105, 769. Dowd, C. A.: Ann. Surg., 1908, 48, 821.

Abdominal puncture was done with the glass needle. A white milky fluid rose in the tube and showed on smear Gram-positive cocci in chains. The following day a laparotomy was performed. The baby's condition was too critical to permit anything more than the evacuation of a large quantity of pus and drainage of the peritoneal cavity. Death occurred on the day of operation. The autopsy showed a diffuse purulent peritonitis. No focus of infection or portal of entry could be found, and the case must be classified as a so-called idiopathic peritonitis in infancy.

This case is particularly interesting because there were no signs of peritonitis. An abdominal tap was done merely because this procedure had been adopted in all acutely ill cases when the diagnosis was in doubt. Baby L. typifies peritonitis in early infancy. Such infants show the signs of marasmus only, and there is nothing either in the history or examination to direct attention to the abdomen. Confronted with this problem the clinician cannot find adequate grounds for suspecting peritonitis; at the same time he cannot exclude such a possibility. Under these circumstances a procedure that reveals the presence of an exudate or gives assurance of its absence may be very helpful.

CASE III.—Baby V., an infant, aged two months, was admitted to the hospital on January 20, 1921, suffering from a lobar pneumonia of three days' duration. On January 27 an empyema of the right chest was discovered and drainage instituted. The following day the abdomen was distended and an abdominal puncture was done. Purulent fluid was obtained and Gram-positive cocci in pairs were found on a smear. The baby's condition was most critical and the usual therapeutic measures offered little hope. At the suggestion of Dr. Witt, of the resident house staff, 25 cc of antipneumococcus serum, Type I, were injected into the peritoneal cavity. The child died the same day, but an autopsy could not be obtained. The culture of the peritoneal fluid developed what was apparently a pneumococcus, but a contaminating organism prevented its isolation and typing.

CASE IV.—Baby M. was delivered on the obstetrical service of the New York Nursery and Child's Hospital February 26, 1921, weighing at birth six pounds thirteen ounces. The infant was transferred to the pediatric service, with a history of a steady decline in weight, refusal of food, vomiting and abdominal distention. After temporary improvement these symptoms recurred, and in addition, on March 21, pus was noted exuding from the umbilicus. The right iliac fossa was chosen as the site for the abdominal tap in order to avoid contamination by the purulent process localized about the umbilicus. Purulent fluid was obtained, but no organisms could be found on the smear, and the culture was sterile. Operation was



considered inadvisable and the baby died on March 24. At autopsy the ascending colon was found to be covered with loose vascular fibrinous adhesions—a localized plastic peritonitis. Whether there was also a generalized peritonitis could not be determined because of the flooding of the abdominal cavity by the intestinal contents, due to a rupture of the duodenum.

CASE V.—Francis R., an infant, aged two months, was admitted to the hospital on March 28, 1921, because of vomiting, refusal of food and an infected umbilicus. On examination the umbilicus was found to be red; the edges pouted and a drop of pus could be expressed. A mass was felt surrounding the umbilicus and extending toward the left flank. An abdominal tap was done. Very little fluid was obtained and two capillary tubes had to be passed into the cannula to get sufficient exudate for two smears and a culture. The smears were crowded with pus cells and a very few organisms in pairs were found. A laparotomy was performed. The peritoneum was found to be thick and indurated, but *there was apparently no free fluid exudate*. The cells of intestine were very red and injected and covered with a loose fibrin. One pole of the spleen was adherent to the peritoneum in the umbilical region and a probe could be passed through the infected umbilicus into the peritoneal cavity. The abdomen was drained. The child died on the day on which he was operated, but an autopsy could not be obtained.

Abdominal puncture in this case was particularly instructive, in that it demonstrated how small an exudate may be revealed by the capillary tube. Although enough fluid was obtained with the capillary tube for smears and culture no free fluid was found at operation but merely a loose edematous fibrin covering the intestinal coils.

The therapy of peritonitis in infancy is extremely unsatisfactory. Indeed, many cases are discovered only at autopsy. The procedure suggested offers the hope of early diagnosis, and this, in turn, may develop more adequate therapy.

**Marasmus.** Fluid was found by abdominal puncture in the peritoneal cavity in 7 of 12 marantic infants (Chart I). As a rule the fluid was clear; only those specimens that contained 1700 or more cells showed a granular turbidity. There is nothing characteristic concerning the cellular elements, which are chiefly lymphocytic. The albuminous content, as judged by the appearance of the smears, must be low; the picture is quite different from that of many pus cells in a heavy albuminous matrix observed in peritonitis.

No reference to an excess of peritoneal fluid in marasmus could be found in the literature.<sup>5</sup> It is hardly conceivable that the occur-

<sup>5</sup> Finkelstein and others mention the occurrence of "hydrops," but this refers to a subcutaneous accumulation of fluid.

CHART I.—ABDOMINAL TAP IN MARASMUS.

Name.	Age.	Weight.	Diagnosis in addition to marasmus.	Condition of abdomen.	Result of tap.	Cell count.	Remarks.
Virginia K.	4	4	.....	Scaphoid	0		
Susan H.	5	8½	Tuberculosis	Not distended	0		
John M.	2½	5½	.....	Slight distention	0		
John S.	4½	8½	Intoxication	Not distended	0		
Lucinde, P.	3½	7½	.....	Not distended	0		
James P.	3½	5½	.	Flat	+	860 cells per c.mm.; 100 counted, all lymphocytes	
Agnes H. July 10, 1920	3	6½	...	.....	0	.....	Two intravenous and one intraperitoneal injection before tap.
Aug. 4, 1920	3½	6	.	Slight distention	+	19 cells per c.mm.; large epithelial? cells	No parenteral fluids for three weeks prior to tap.
Aug. 18, 1920	4	5½		.....	+	2600 cells per c.mm.; polynuclears, 40 per cent; lymphocytes and "epithelial," 60	Two hypodermoclyses and one intravenous but no intraperitoneal injections given.
John H.	3½	6½		Slight distention	+	Polynuclears, 14 per cent; lymphocytes, 86 per cent	
Catherine O'L.	3½	6½		Soft; not distended	+	290 cells per c.mm.; polynuclears, 81 per cent; lymphocytes, 19 per cent	
Cynthia L.	4½	6½	Rickets; tuberculosis suspected	Slight distention	+	850 cells per c.mm.; polynuclears, 9 per cent; lymphocytes, 91 per cent	
William W. Joseph B. Aug. 18, 1920	3½	5	..	Slight distention	+	1700 cells per c.mm.	
Oct. 11, 1920	7	5½	Bronchopneumonia		+	630 cells per c.mm.; polynuclears, 20 per cent; lymphocytes, 80 per cent	
					+	2300 cells per c.mm.; polynuclears, 4 per cent; lymphocytes, 75 per cent; "epithelial," 21 per cent	

rence of a large ascites could have been constantly overlooked in all the previous careful pathological studies. Our own autopsy protocols during the past months, when our interest was centered on this question, do not record appreciable quantities of peritoneal fluid in marantic infants. And, indeed, the results reported here do not imply the presence of a large ascites. This method—the use of the capillary tube—demonstrates very slight deviations from the normal. In the normal infant no fluid can be found by this procedure,<sup>6</sup> and under conditions simulating an effusion, Denzer and Anderson have found that the capillary tube shows the presence of from 5 to 15 cc of free peritoneal fluid.<sup>7</sup> Furthermore, there is no evidence clinically of a large ascites; neither fluid wave nor shifting dulness could be elicited in our marantic infants. Thus all the available data suggest that the transudate demonstrated by the capillary tube in marantic infants is extremely small.

The clinical significance of this transudate is not apparent. There is no relation between the occurrence of fluid and the severity of the disease. Likewise, there are no constant physical findings associated with the presence of an ascites. As mentioned previously, there is not sufficient fluid to produce the usual signs of ascites, nor can distention be correlated with the peritoneal transudate. In only one case in which a positive tap was obtained had an intraperitoneal injection been done prior to the puncture.<sup>8</sup> However, the ascites is sufficiently constant to be considered part of the pathological picture of marasmus.

Speculation as to the role which ascites plays in marasmus would involve the whole question of its pathogenesis, and that in turn the complicated problem of water metabolism. Such speculation would probably be fruitless, and it therefore seems advisable merely to record the fact that in a certain percentage of marantic infants an excess of peritoneal fluid is found.

**Rickets.** In 4 of 8 cases of rickets abdominal tap showed the presence of fluid in the peritoneal cavity (Chart II). In one case (Marie O'D.) the glass needle was used and 1 cc of fluid collected. The cells range in number from 100 to 1000. A differential smear shows a predominance of lymphocytes; the microscopic picture, however, is not characteristic and cannot be distinguished from that found in marantic infants.

The series is not sufficiently large to warrant conclusions concern-

<sup>6</sup> Writers on the anatomy and physiology of the peritoneum agree that there is merely enough peritoneal fluid to lubricate the abdominal contents—that normally there is no “free” peritoneal fluid. Indeed, no analyses of “normal” peritoneal fluid have ever been made because it is impossible to collect enough for chemical examination.

<sup>7</sup> The Absorption of Fluid Injected into the Peritoneal Cavity, *Am. Jour. Dis. Children*, June 2, 1921, 21, 565.

<sup>8</sup> Agnes H. received an intraperitoneal injection three weeks prior to the first positive tap.

ing the cause of the ascites. The occurrence of pot-belly in most of the cases that showed free fluid suggests that the mechanical and circulatory derangement incident to the large abdomen may play some part in the development of the ascites. However, this is merely an impression, and further work will be necessary both to determine the incidence of free fluid in rickets and to explain its pathogenesis.

CHART II.—ABDOMINAL TAP IN RICKETTS.

Name.	Age.	Weight.	Pot belly.	Result of tap.	Cell count.
Isaac S. . .	11	14½	Very slight	+	Small amount; enough for few smears only.
Stewart, S. . .	5	11½	None	0	
David D. . .	4	27	None	0	
Arnold M. . .	19	....	Moderate	0	
Doris J. . .	17	17	Very slight	0	
Marie O'D. Sept. 20, 1920	6	8½	Very marked	+	350 cells per c.mm., lymphocytes, 85 per cent, polynuclears, 15 per cent.
Mar. 10, 1921	11	....	Very marked	0	
Leon T. . .	4	9½	0	+	1000 cells per c.mm.; lymphocytes, 95 per cent; polynuclears, 5 per cent.
Hazel R. . .	8	11	Marked	+	

**Summary.** Five cases of peritonitis are presented in which abdominal puncture and the capillary tube were of service in establishing the diagnosis. The same method has revealed free fluid in the peritoneal cavity of cases of rickets and marasmus, a finding which, as far as I have been able to determine, has not been recorded previously. These observations on peritoneal inflammations and transudates are not numerous enough to warrant sweeping generalizations. They are important because they indicate that a procedure which demonstrates minute amounts of fluid in the peritoneal cavity may be helpful in answering many questions of practical and experimental interest—the initial response of the peritoneum to infectious and other irritants, the question of peritoneal absorption and the therapeutic use of sera in pneumococcic infections. The method of abdominal puncture with the use of the capillary tube has passed the experimental stage; a larger experience is necessary to disclose its possibilities and define its limitations.

I wish to thank Dr. A. F. Anderson and Dr. D. B. Witt, respectively resident and assistant resident physicians at the New York Nursery and Child's Hospital, for their kind coöperation in the selection of some of the cases and the performance of the punctures.

# SOME STATISTICS CONCERNING PNEUMONIA AND EMPYEMA IN CHILDREN.

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THIS report was compiled at the request of Dr. J. P. Crozer Griffith, who was interested in the incidence of empyema after hospital-treated pneumonia. The total number of cases diagnosed as pneumonia in the children's ward of the University Hospital, Philadelphia, in the years 1900 to 1918 inclusive was 611. Children are admitted to this ward up to the age of thirteen years. The series includes the cases admitted with a primary pneumonia, those in which pneumonia occurred as a complication and influenzal pneumonias. I have excluded the cases of empyema reported in a previous paper on this subject which were admitted to the hospital on the surgical service.

The statistics of pneumonia which were necessarily collected in the material for this report are of enough significance to warrant their inclusion.

The frequency of the type of pneumonia is given in Table I. In the pneumonia of children it is often difficult to state definitely the type of the process, therefore the following figures are only approximately correct. Some of the cases might have been placed in the other group by another clinician.

TABLE I.—INCIDENCE OF PNEUMONIA.

Bronchopneumonia . . . . .	274
Croupous pneumonia . . . . .	312
Non-specified . . . . .	25
Total . . . . .	611

In Table II the incidence of broncho- and croupous pneumonia is given according to the age and sex. Charts I and II graphically express this. There is no distinction drawn in the admission of males and females to the children's ward. The total admissions to the ward in two years chosen at random showed a greater number of females than males, therefore the predominance of males in both the broncho- and croupous pneumonias cannot be ascribed to sex preference in admission or to the occasional quarantine of the ward to females because of outbreaks of vaginitis. In both types of pneumonia there is a rise in incidence during the second year. The increase in the percentage at this age is enough to be of some significance.

The well-known fact that bronchopneumonia is more frequent than croupous in infancy is well brought out by these figures, there being a difference of 12.8 per cent in the first six months and 8.2 per cent in the last six months of the first year. After the fourth

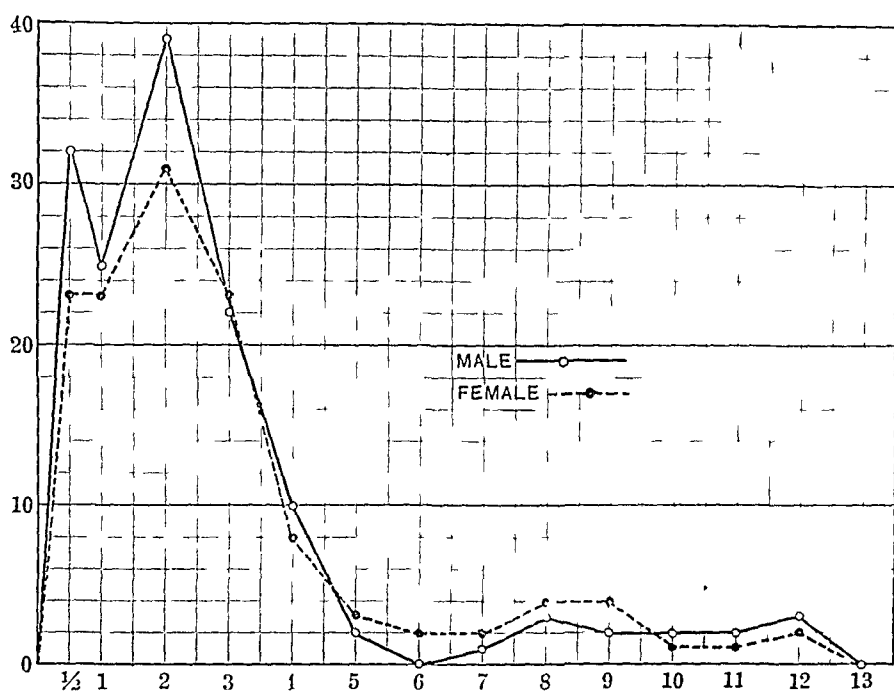


CHART I—Age and sex incidence of bronchopneumonia

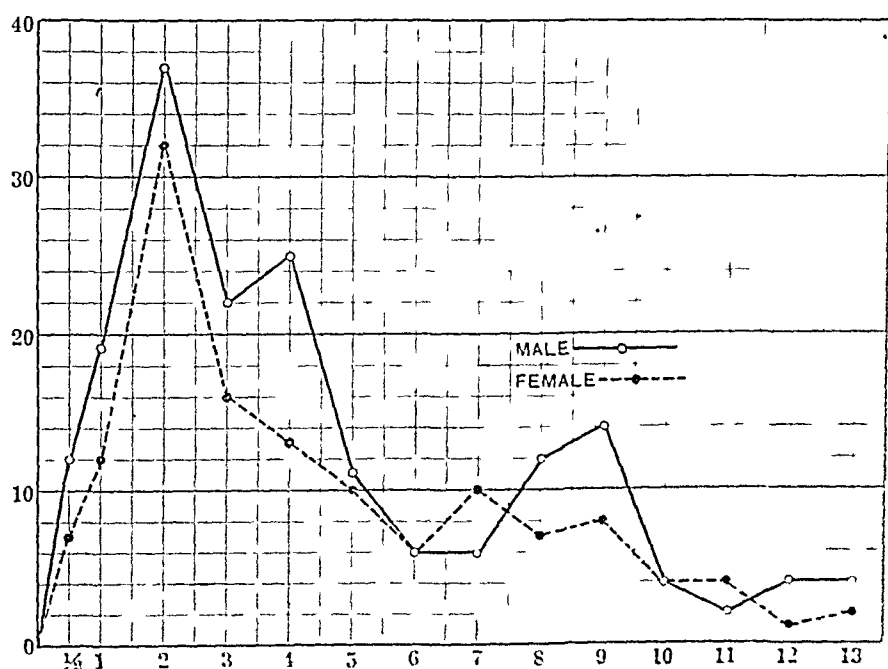


CHART II.—Age and sex incidence of croupous pneumonia

year bronchopneumonia was relatively infrequent in this series of cases.

TABLE II.—AGE AND SEX INCIDENCE OF PNEUMONIA.

Age.	Bronchopneumonia.				Croupous pneumonia.			
	No. of cases:		Percentage of total:		No. of cases:		Percentage of total:	
	Male.	Female	Male.	Female.	Male.	Female	Male.	Female.
1 to 6 months . . .	32	23	22.3	18.1	12	7	6.7	5.3
6 mo. to 1 yr. . .	25	23	17.4	18.1	19	12	10.6	9.09
1 to 2 years . . .	39	31	27.2	24.4	37	32	20.7	24.2
2 to 3 years . . .	22	23	15.3	18.1	22	16	12.3	12.1
3 to 4 years . . .	10	8	6.8	6.2	25	13	14.04	9.8
4 to 5 years . . .	2	3	1.3	2.3	11	10	6.1	7.5
5 to 6 years . . .	0	2	0	1.7	6	6	3.3	4.5
6 to 7 years . . .	1	2	0.6	1.7	6	10	3.3	7.5
7 to 8 years . . .	3	4	2.09	3.1	12	7	6.7	5.3
8 to 9 years . . .	2	4	1.3	3.1	14	8	7.8	6.05
9 to 10 years . . .	2	1	1.3	0.78	4	4	2.2	3.02
10 to 11 years . . .	2	1	1.3	0.78	2	4	1.1	3.02
11 to 12 years . . .	3	2	2.09	1.7	4	1	2.2	0.75
12 to 13 years . . .	0	0	0.00	0.0	4	2	2.2	1.5
Total . . .	143	127			178	132		

The mortality for the series is 30.2 per cent. Table III gives the mortality by age and sex. In both varieties the mortality percentage decreases, with two exceptions as the age increases. This percentage has been omitted for the years in which the number of cases in our series was so small as to make the results misleading. There is a marked contrast in the total mortality in broncho- and croupous pneumonia, the mortality percentage for the former being 39.4 and for the latter 18.3. One obvious reason for this marked difference is the fact that bronchopneumonia occurred as a terminal complication in a number of cases. Complicating empyemata have not affected this mortality, for the occurrence of empyema after bronchopneumonia is infrequent.

TABLE III.—MORTALITY IN PNEUMONIA.

*A. Mortality by Age and Sex.*

Age	Bronchopneumonia.				Croupous pneumonia.			
	No. of deaths.		Mortality percentage		No. of deaths.		Mortality percentage	
	Male.	Female	Male.	Female.	Male.	Female	Male.	Female.
1 to 6 months . . .	18	17	56.2	73.9	5	4	41.3	57.1
6 mo. to 1 yr. . .	14	14	56.0	60.8	7	4	36.8	33.3
1 to 2 years . . .	16	12	41.02	36.5	10	8	27.02	25.0
2 to 3 years . . .	6	12	27.2	52.1	3	3	13.6	18.7
3 to 4 years . . .	0	0	.....	.....	4	1	16.0	7.8
4 to 5 years . . .	0	0	.....	.....	2	0		
5 to 6 years . . .	0	1	.....	.....	1	0		
6 to 7 years . . .	0	0	.....	.....	0	1		
7 to 8 years . . .	0	2	.....	.....	1	0		
8 to 9 years . . .	1	3	.....	.....	1	0		
9 to 10 years . . .	1	0	.....	.....	0	0		
10 to 11 years . . .	0	1	.....	.....	0	0		
11 to 12 years . . .	2	0	.....	.....	0	0		
12 to 13 years . . .	0	0	.....	.....	0	0		
Total . . .	58	62			34	23		

*B. Group Mortality.*

Age.	Bronchopneumonia.			Croupous pneumonia.		
	Number of		Percentage of deaths.	Number of		Percentage of deaths.
	Cases.	Deaths.		Cases.	Deaths.	
Under 2 years . . . . .	173	91	52.6	119	38	31.9
2 to 5 years . . . . .	68	18	27.9	97	13	13.4
5 to 13 years . . . . .	29	11	37.9	94	6	6.3

Some prognostic significance has been attached to the location of the pneumonia process in the lobar pneumonia of adults. For this reason Table IV is included. The mortality is highest in the cases in which one entire lung is involved, the right side showing the higher mortality. The right upper lobe is more frequently involved and has a higher mortality than the left upper lobe, while this is reversed for the bases.

The sites of the lesions in the cases of bronchopneumonia have not been tabulated because almost invariably there were areas of pathology in both lungs.

TABLE IV.—LOCATION OF THE LESIONS IN CROUPOUS PNEUMONIA.

	Number of times involved.	Deaths.	Percentage of deaths.
Left upper lobe . . . . .	22	1	4.5
Left lower lobe . . . . .	63	7	11.1
Entire left lung . . . . .	31	7	22.5
Right upper lobe . . . . .	68	6	8.8
Right lower lobe . . . . .	51	5	9.8
Right middle lobe . . . . .	6	0	
Entire right lung . . . . .	45	16	35.5
Both apices and left base . . . . .	4	2	
Both apices . . . . .	3		
Left apex and right base . . . . .	2	1	
Right upper and middle lobes . . . . .	2		
Entire left lung and right apex . . . . .	2	1	
Whole right lung and left base . . . . .	1	1	

The difference in the percentage of empyemata following broncho- and croupous pneumonias cannot be accounted for by the difference in the total number of cases. However, the fact that a number of the bronchopneumonias were terminal must be considered. In Table VI a correction is made for this fact by subtracting from the total number of cases of bronchopneumonia those which died during the acute process. Although the percentage of empyemata after bronchopneumonia is lower the mortality in this type of empyema is much higher.



TABLE V.—FREQUENCY OF EMPYEMA IN PNEUMONIA.

		Per cent.
Number of empyemata following bronchopneumonia . . . . .	5	1.8
Number of empyemata following croupous pneumonia . . . . .	22	7.5
Number of empyemata following unspecified pneumonia . . . . .	12	
Total number of empyemata in 611 cases of pneumonia	39	

TABLE VI.—CORRECTED PERCENTAGE OF INCIDENCE OF EMPYEMA.

Percentage of empyemata after bronchopneumonia (deaths during acute pneumonia process subtracted) . . . . .	3.14
Same correction for croupous pneumonia . . . . .	8.59

TABLE VII.—MORTALITY IN POSTPNEUMONIC EMPYEMA.

		Per cent.
Number of deaths following bronchopneumonia empyemata . . . . .	4	80.0
Number of deaths following croupous pneumonia empyemata . . . . .	8	36.3
Total number of deaths in 39 cases of empyema . . . . .	15	38.4

A slight discrepancy in a comparison of the figures of the various tables is due to the omission of cases in which all the data necessary was not present in the history.

## UNKNOWN FORMS OF ARTERITIS, WITH SPECIAL REFERENCE TO THEIR RELATION TO SYPHILITIC ARTERITIS AND PERIARTERITIS NODOSA.

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COMPARATIVELY little is known about arteritis and its significance if we disregard syphilitic endarteritis, which is well known, and tuberculous arteritis in the meninges associated with exudation, which is the dominant feature. Otherwise but little has been written about arteritis until rather recently. According to Spiro,<sup>1</sup> French authors, and later Wiesel and v. Wiesner, described peculiar inflammations or rather necroses in the small arteries, particularly in the heart, in measles, scarlet fever, diphtheria, suppurative processes, etc., which result in scars and are believed to favor the development of coronary sclerosis, but apparently these observations have attracted but little attention. More recently the vascular changes in infections and intoxications have been studied more closely. Thus Herzog<sup>2</sup> describes the following changes in poisoning with illuminating gas: Hyaline swelling of the walls of the small

<sup>1</sup> Virchow's Arch., 1920, No. 227.

<sup>2</sup> München. med. Wehnschr., 1920, No. 19.

arteries in the brain with proliferation of the endothelium and hyaline thrombosis, followed later by calcification and softening of the brain tissue. Similar changes with calcification have been described as occurring quite early by Geipel and Schmorl,<sup>3</sup> the small arteries in the lenticular nucleus being especially involved. Similar changes may occur in other forms of poisoning, *e. g.*, hydrocyanic acid, salvarsan and phosgen gas, but it really does not concern any arteritis.

In various infectious diseases inflammatory vascular changes may occur, as seen especially in the cerebral vessels in influenza with hemorrhages, which, however, seem to depend largely on degenerative changes.<sup>4</sup> Markus<sup>5</sup> describes infiltration with cells in the wall of the vessels in the pia in influenza, and Stoerck and Epstein<sup>6</sup> describe necrosis and degeneration with reparatory processes in influenza, resembling the changes in arteriosclerosis. Of greater interest are the changes that have been found in the vessels of the skin in typhus by Frankel<sup>7</sup> and others. Nicol<sup>8</sup> describes these changes as involving the capillaries and precapillary arteries in most of the organs, with partly exudate, partly proliferative changes as well as necrosis. Inflammatory and degenerative changes occur also in the small vessels in the skin in epidemic meningitis, and Weiss and Stufeland<sup>9</sup> describe certain changes in the capillaries of the skin in scarlet fever.

While engaged in the examination of microscopic preparations from a large amount of anatomical material I met with occasional peculiar lesions in the vessels that do not correspond to the usual forms, and on this account I have thought it worth while to describe some of the cases with some detail.

*CASE I.—Idiopathic Renal Hemorrhage.* This concerns a kidney which was removed from a man, aged twenty-two years, who for about one year had suffered from frequent hemorrhages from the one kidney and later from pain. Macroscopically the kidney appeared normal, but microscopically there were found necrotic foci throughout the kidney, in the center of which were arteries with swollen walls and narrowing of the lumen. The swelling was due to proliferation of the intima and to hyaline changes in the connective and elastic tissue, while the surrounding renal tissue frequently was necrotic, there being, however, no sign of inflammation.

The cause and nature of the changes in the arteries were obscure. Syphilis was excluded and it hardly concerned arteriosclerosis.

<sup>3</sup> München. med. Wchnschr., 1920, No. 43.

<sup>4</sup> Harbitz: Norsk. Mag. f. Lægevidenskapen, 1920.

<sup>5</sup> Ztschr. f. Neurol. u. Psych., 1920.

<sup>6</sup> Frankf. Ztschr. f. Pathol., 1920, No. 23.

<sup>7</sup> München. med. Wchnschr., 1914, 1915, 1917.

<sup>8</sup> Ziegler's Beiträge, 1919, No. 65.

<sup>9</sup> Ibid., 1918.

The case might be regarded as a local form of periarteritis nodosa, especially in view of the necroses in the media and the proliferation of the intima. That the lesion of the arteries, which involved also vessels in the papillæ, was the cause of the hemorrhage seems altogether reasonable, and in that case it hardly would be correct to speak of the case as one of "idiopathic hemorrhagè," as the hemorrhages had an organic basis.

CASE II.—*Purpura Rheumatica*. This concerns a man, aged forty years, who died with the clinical picture of "purpura rheumatica" about two months after the beginning of the illness. At postmortem there was found extensive thrombosis (inferior vena cava, in the left iliac and the left femoral vein, hepatic vein with infarct in the liver, and also in several sinuses of the dura with large hemorrhagic infarcts in the brain). In the skin there was no evident exanthem, but extensive infiltrations of leukocytes, lymphocytes and red corpuscles as well as pure hemorrhages. There was also extensive changes, in the smaller bloodvessels and arteries as well as veins, with cellular infiltrations in the walls and necrosis. The intima was swollen and there was often thrombosis. These changes were most marked in the arteries, medium sized and small. The veins were not so markedly involved, but there was more or less necrosis and infiltration as well as thrombosis.

In this case syphilis may be excluded. The cutaneous infiltrations and the thrombosis were more extensive than is the case in exanthematic typhus, a disease that so far as known has not occurred in Christiania for many years. As regards periarteritis nodosa it should be noted that there were no typical nodular formations in the walls of the vessels and that the infiltrations were larger and more extensive than [is the case in that disease. Hence it seems most reasonable to assume the presence of some unknown form of infection. Bacteria were not demonstrable by the usual methods.

CASE III.—*Peculiar Disease of Cerebral Arteries* (Figs. 1 to 3) A woman, aged twenty-six years, of doubtful habits. She had suffered much with headache since early in life; during the last two years she had had attacks of fainting off and on, and about a year and a half ago she received a blow to the head during such an attack. In the autumn of 1917 the hands became tremulous; even earlier she had had double vision and sometimes vestibular attacks, with vomiting as well as convulsive movement of the face. In the autumn of 1918 she had influenza and became worse afterward, with pain in the legs, difficulty in walking and convulsive attacks of a hysterical nature. In March, 1919, she was examined by Dr. Svenson, who reports as follows: Dull; rather stuporous; somewhat disoriented; speech monotonous; eyes normal; no symptoms on the part of the cranial nerves, pons or bulb. Reduced strength

in the arms; ataxia; spastic paraparesis of both legs with increased patellar reflexes and positive Babinsky sign; Romberg's symptom present; uncertain, spastic walk, but no disturbances of sensibility.

She became bed-ridden, with increasing stupor, headache, choked disk and increasing paresis in the extremities.

The disease was first regarded as a multiple sclerosis, but later, as signs of increasing brain-pressure developed, a tumor of peculiar localization and secondary hydrocephalus was considered. The patient became finally completely comatose, with muscular rigidity, fever, albuminuria and pneumonia. Death on May 19, 1919.

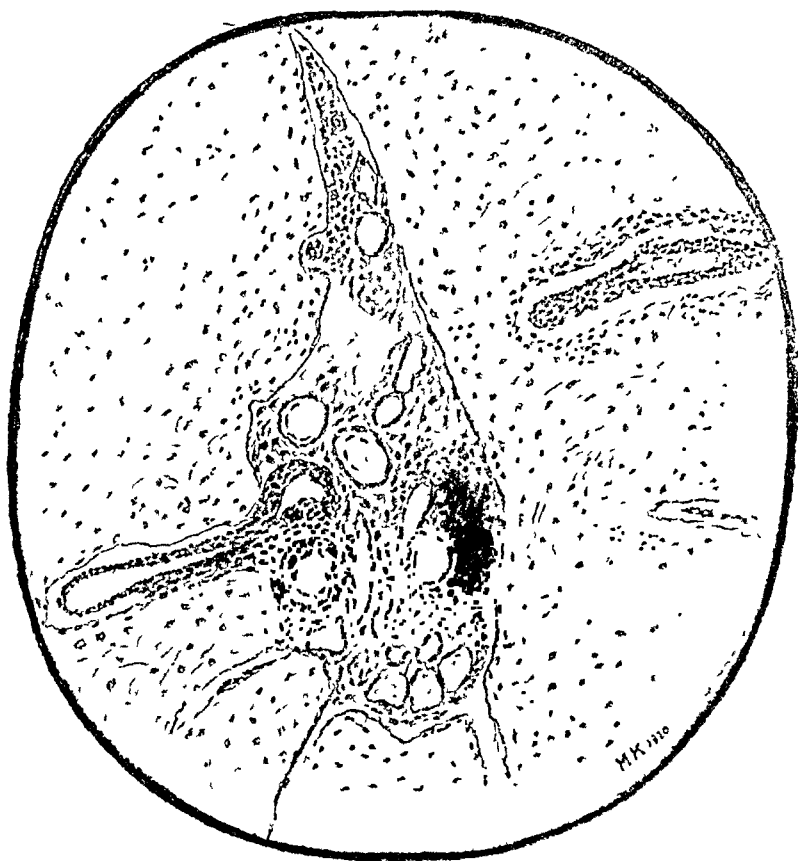


FIG. 1.—Extensive infiltration in the bottom of a sulcus, especially about the arteries, whose walls are thick and partly necrotic; some giant cells.

Only the brain was examined. There was injection of the membranes. In the floor of the lateral ventricles, particularly the left, were areas of a solid, rather tumor-like infiltrations; in the central ganglia were recent areas of hemorrhage, of the size of hemp seeds, and in the centrum semiovale on the right side was a hemorrhage as large as a hen's egg, the surrounding tissue being apparently hardened; there were diffusely infiltrated areas in the corpus callosum also.

The microscopic examination revealed an inflammatory process in the pia arachnoid and in the brain closely related to the bloodvessels, particularly the arteries, and following the bloodvessels from the pia inward into the brain substance. The changes were present seemingly everywhere, also at the base and in marked degree in the central ganglia. There was a remarkable widening of the bloodvessels with hemorrhagic infiltration in various places in the brain. In the pia arachnoid the inflammation was closely related to the smaller arteries and their branches into the cortex, there being no diffuse changes. The inflammatory cells were principally lymphocytic. The process extended inward from the sulci;

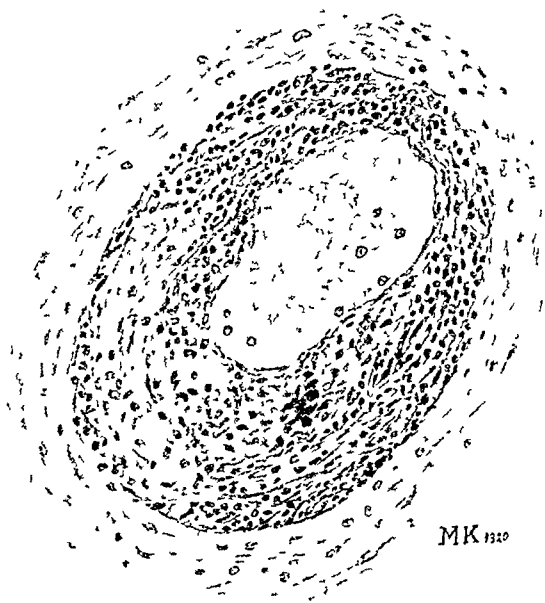


FIG 2 —A smaller arterial branch in the surface of the brain severely infiltrated, structure not clear, partly obliterated, necrosis of intima and media.

the veins were dilated and the walls infiltrated with lymphocytes, usually diffusely, but the arterial walls were more involved, being thickened, infiltrated with lymphocytes and leukocytes as well as larger cells at the same time as the connective-tissue cells in the intima and of the adventitia had proliferated, the result being a thick ring around a wide lumen. In the dense infiltration were many larger and smaller multinucleated giant cells. There was no marked necrosis. In many places the process extended throughout the whole segment of the vessel, but in other places the segment was only partially involved. Smaller arteries might be practically closed and in the remnant of the lumen thrombi were present. Among the epithelioid cells were lymphocytes and also different

kinds of plasma cells as well as yellow iron-containing pigments in amorphous masses or enclosed in larger cells. In the central ganglia there was the same picture with in places pure hemorrhages. The lumen of the arteries might be filled with epithelioid and giant cells, the process being perhaps more intense here than elsewhere, usually focal but also more diffuse throughout the arterial walls as well as beyond. The cells were mostly mononuclear, but there

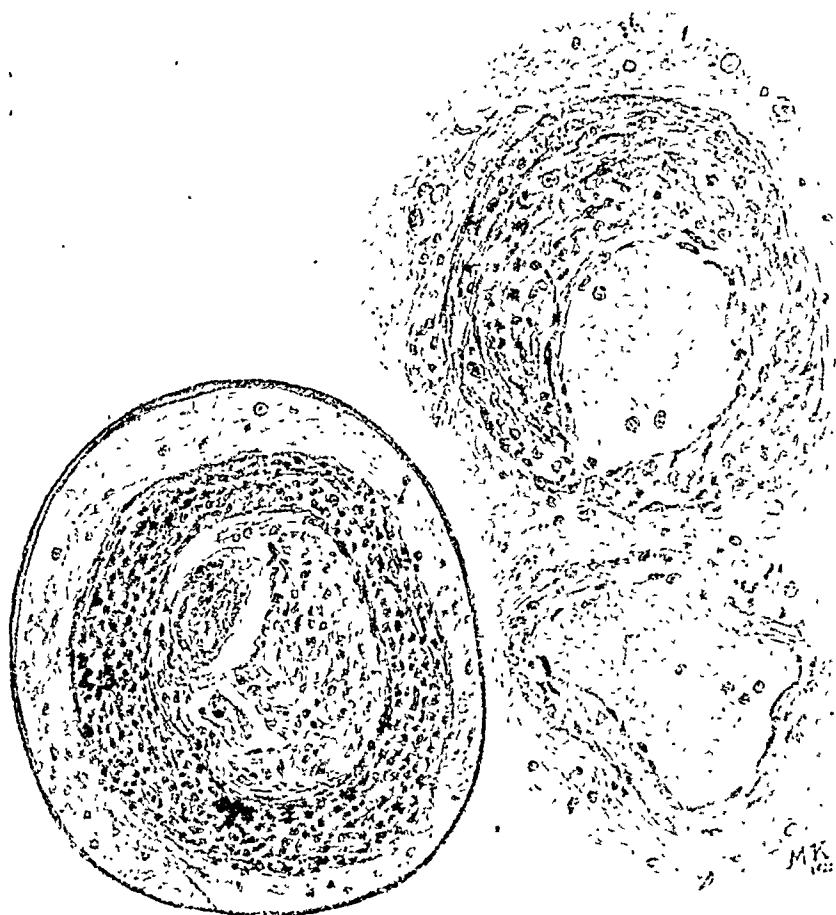


FIG. 3.—The vein (below to the right) shows some inflammation, but the two arteries are extensively infiltrated and there is proliferation, especially in the intima of one of them; in the other the lumen is closed and there are two giant cells among the epithelioid cells; some necrosis in the media.

were also plasma cells and polymorphonuclear leukocytes, sometimes in large masses. There were no necrotic foci, but in the neighborhood of the severely involved vessels the ganglia cells showed degeneration in varying degrees.

No microbes could be demonstrated in the sections (Loeffler's method, Gram's method, stains for the tubercle bacillus and Levaditi's method for spirochetes).

In this case we have a chronic cerebral disease in a woman, aged

twenty-six years, of uncertain nature, so that no definite clinical diagnosis could be made, although the manifestations clearly pointed more and more to organic brain lesion. To the naked eye the appearances in the brain were also puzzling, their being no definite meningitis, the most striking feature in the brain substance being larger and smaller hemorrhages and infiltrations both on the surface and in the deeper parts. The microscopic examination demonstrated a diffuse and marked inflammatory process connected especially with the arteries, the essential lesion being arteritis, but of what kind? It would seem that the anatomical picture does not correspond to that of any known disease. Lethargic encephalitis is different both as to localization and the kind of inflammatory process, especially in that in this disease it does not concern a primary arterial affection. And then the clinical picture does not correspond to that of lethargic encephalitis. Cerebral syphilis must be considered: Spirochetes were not found, and it is noteworthy that the anatomical lesions differ from those of syphilis. The history does not indicate syphilis (Wassermann's test was negative). There were no gummatous changes. Syphilitic endarteritis, as a rule, does not appear as a diffuse process being generally confined to the larger branches, particularly at the base, and to limited vascular areas, being accompanied generally with thrombosis and narrowing, so that necrosis and softening of the corresponding parts of the brain take place. The hyperemia, the dilatation and infiltration of the veins and the multiple hemorrhages do not correspond to the usual picture of syphilis of the cerebral vessels. The absence of necrosis and caseation speak against syphilis while the marked proliferation of the intima with formation of giant cells remind one somewhat of syphilitic endarteritis. At the same time the intima did not show the marked proliferation usually found in syphilis and, on the other hand, the media was more torn apart than is usual in syphilis. The possibility of syphilis may not be excluded, but the entire clinical picture, together with the anatomical lesions, must be said to go against syphilis.

In periarteritis nodosa the clinical phenomena are variable. Practically all organs may become involved. The duration in this case is longer than seen in periarteritis nodosa, but of course that does not exclude it. It is more important to note that the cerebral arteries are rarely involved in periarteritis nodosa, only two cases being described in the literature. Chovstek and Wechselbaum<sup>10</sup> in 1877. described a case in a soldier, aged twenty-three years, who died after seven months of illness with marked cerebral symptoms and in whom the principal cerebral arteries showed multiple aneurysms. And Müller<sup>10</sup> records a similar observation in a man, aged thirty-two years, who was ill for six or seven months with cerebral

<sup>10</sup> Müller, P., Festschr. z. Feier d. 50 jährigen Bestehen der Stadtkrankh., Dresden-Friedrichsstadt, 1899.

and ocular symptoms. To the naked eye there were only scattered hemorrhages of the brain, but microscopically there was inflammatory infiltration in the walls of the vessels with narrowing of the lumen and necrosis and hyaline degeneration of the walls; the arteries in other organs were involved in the usual manner. None of these cases, however, resemble the one I have described when close comparison is made. Furthermore, there were no nodules or aneurysms in my case. The marked thickening and necrosis in the media, which is so characteristic of periarteritis nodosa, being regarded by many as the primary anatomical lesion, was absent in my case.

While neither syphilis nor periarteritis nodosa, as a rule, does not show the anatomical lesions described in this case, they may hardly be definitely excluded, especially not syphilitic endarteritis.

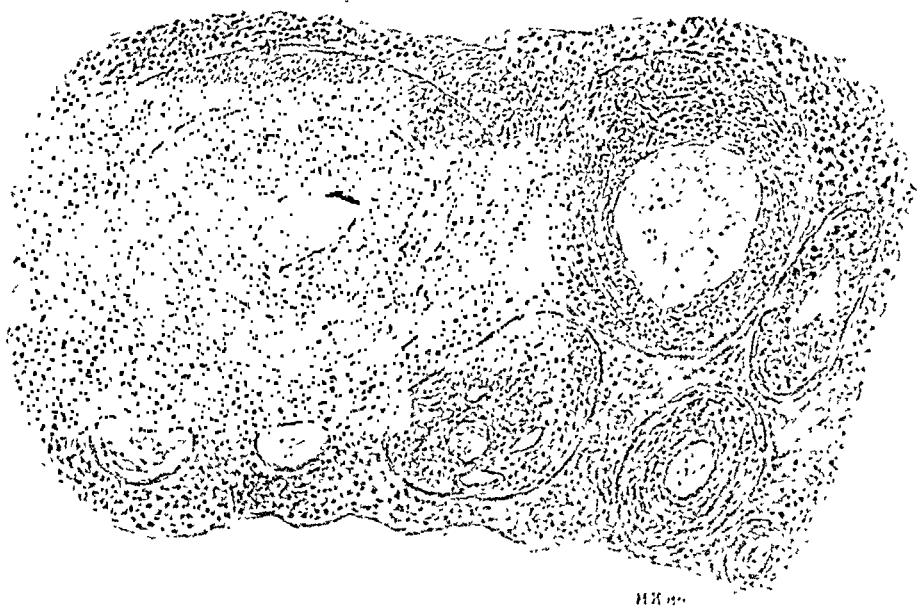


FIG. 4.—Extensive inflammatory changes in small veins and arteries in the bottom of a sulcus, with narrowing and closure of the lumen.

CASE IV.—*Cerebral Arteritis with Mental Disturbances* (Figs. 4 to 6). A sailor, aged forty-six years, was placed in an insane hospital (Dr. Platou) in January, 1919, on account of confusion and hallucinations. He made peculiar movements, *v. g.*, swimming movements, both when standing and when lying down, and would have attacks of violence for a day or so followed by periods of mental clearness, and in the latter part of March he was discharged as cured. It was thought that alcoholism was at the bottom of his trouble.

In June he began to suffer from attacks of fainting, dizziness, vomiting, and later of impulsive violence, when he wanted to kill



his sister, and in August he was again confined. He was restless and talked a great deal of nonsense; the right pupil was larger than



FIG. 5.—All layers of arterial branch extensively involved.

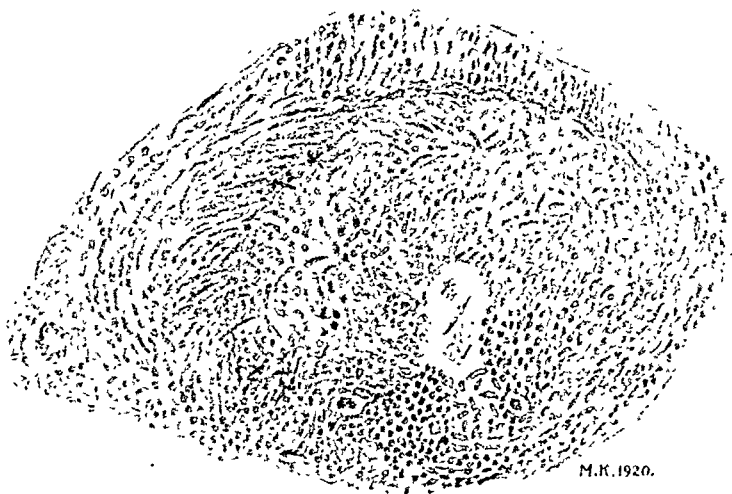


FIG. 6.—Note giant cells and extensive infiltration.

the left, but reacted to light and accommodation; a little later the left face seemed to be paralyzed. He had had chancre in 1904, but the Wassermann was negative. In the middle of September he

was completely disoriented, could hardly walk and was soporous. Death on September 30.

No definite diagnosis was made, but it was thought that the psychosis depended on an organic brain disease.

The postmortem showed no special changes in the heart or arteries; mucopurulent bronchitis in the right lung; liver and kidneys normal; no special changes in the lower urinary tract or in the digestive organs; no tuberculosis anywhere.

The dura showed a growth as large as a hazelnut extending inward into the brain in gyrus centr. ant. sin. The pia arachnoid was thick and adherent. In the upper part of the left temporal lobe was a soft mass including a nodule as large as a walnut; there were several growths of hazelnut size in both hemispheres, of firm consistency; no sclerosis in the vessels; ventricles not dilated.

Some of the growths were subjected to careful microscopical examination. It was found that vessels extended into the center of the growths; the vessels were thick and the lumen narrowed, in places thrombotic. There were no tubercles or larger caseous or gummatous infiltrations as are characteristic of syphilitic meningo-encephalitis. It concerned an inflammatory process concentrated about and proceeding from the bloodvessels and extending into the brain substance, which was edematous and hyperemic, with dilated vessels, and an inflammatory infiltration extended outward into the brain substance from the affected vessels. It was characteristic that these infiltrations all involved the surface of the brain, or rather the pia arachnoid, from which the process extended into the brain. The process may be described more minutely as follows: From the surface of the brain the infiltration would pass down between two gyri, increase in thickness so that it would form a mass in the bottom of the sulcus and extend into the substance along the vessels; in the center would be recognized the contour or remnants of several larger vessels, completely obliterated, in a partly necrotic, extremely cellular tissue, smaller infiltrations extending farther along widened vessels with infiltrated walls. The infiltration consisted of rather large mononuclear cells, lymphocytes, plasma cells, eosinophile cells, but, as a rule, without any polymorphonuclear leukocytes, but in places would be cells with fat granules. Extending into the brain substance the infiltration was principally perivascular, consisting mostly of mononuclear cells. The most striking feature was the involvement of the medium-sized arteries in the sulci and of their branches into the brain, the veins being also involved but in less degree. All the coats of the arteries were thickened and infiltrated, the intima being so greatly thickened that the lumen might be completely obliterated. This change of the intima seemed to be due largely to proliferation of its connective-tissue elements, less to invasion of other cells. In some of the smaller arteries were found multinuclear giant cells, rather small,

the nuclei partly central, partly peripheral, partly diffusely scattered over the cells, which occurred especially in the peripheral layer, and intima. In the most severe lesions the different layers of the arteries would disappear, leaving only the outlines of the vessels in the midst of necrotic granular material, but nowhere was there any arrangement like that in tuberculosis or definitely caseous foci. The involvement of the veins was less marked; in places the veins were thrombotic, and in larger necrotic areas they were also necrotic. Surrounding larger masses the small vessels of the brain were greatly dilated and congested.

It would seem that the brain lesion described in this case was the cause of the mental disturbances during life. It is more reasonable to take this view than to believe that in addition to the changes described there had existed also a separate and distinct mental disease. But the principal question is, What kind of arterial disease was this? The first thought was that it concerned a tuberculous process. The vascular infiltrations with the numerous giant and epithelioid cells might point in this direction, but real tubercles or typical tuberculous granulation tissue was not found and tubercle bacilli could not be demonstrated, nor was there any tuberculosis in other organs, hence we are forced to conclude that it does not concern a tuberculous process. Lethargic encephalitis is contraindicated both by the clinical symptoms, the localization and character of the lesions. In fact, no changes such as have been observed in the various stages of this disease were found in the case under consideration. The possibility of syphilis must be considered. There is the history of chancre in 1905; it is true that the Wassermann reaction of the blood serum was negative, but this of itself hardly excludes syphilis. The absence of syphilitic changes elsewhere do not necessarily exclude syphilis. The vascular process resembles in many ways syphilitic arteritis; proliferation of the intima resembles the syphilitic, although perhaps not so marked; the cellular infiltration in the other vascular coats also remind one of syphilis; and numerous giant cells do not exclude syphilis, although they are more numerous here than usual. Against syphilis we have the marked thickening and necrosis of the media and adventitia and the disintegration and destruction in places of the elastic tissue in the media. Spirochetes were not found, but it is difficult indeed to demonstrate spirochetes even in definitely syphilitic vascular processes. The localization is not inconsistent with syphilis, but a widespread process is rare in syphilis, and it would be expected that gummatous and caseous foci would be found in case it concerned syphilis, but they were absent. We see that while important arguments may be brought forward against syphilis it cannot be definitely excluded.

The localization speaks against periarteritis nodosa. With the exception of the cases described by Chvostek and Weikselbaum

and Müller,<sup>10</sup> practically all descriptions of this disease state that the arteries of the brain are not involved. However, the lesion itself corresponds quite closely to that of periarteritis nodosa, the extensive necrosis of the media with separation and destruction of the elastic tissue being marked, but in many cases the necrosis was even more extensive than usual in periarteritis nodosa, and giant cells, which were very numerous in this case, are found only rarely in this disease, the principal changes of which, after a duration of say nine months, appear to be proliferation of the intima and media with necrosis and degeneration, with but little cellular infiltration in the vessel wall and no giant-cell formation (Gruber,<sup>11</sup> Abramof<sup>12</sup> and v. Haun,<sup>13</sup> see also my Case VII). In no case was there such marked necrosis as in my Case IV, and no giant cells, but numerous epithelioid cells. It remains to point out that there were no definite or typical aneurysms in this case. Taking everything into consideration it must be acknowledged that in many ways this case reminds one of periarteritis nodosa, but even more of syphilitic endarteritis.

For purpose of comparison I shall now describe a case of cerebral syphilis with vascular changes of a peculiar character and of special interest in this connection.

CASE V.—A man, aged forty-two years. According to Dr. S. Höyer he began to have pain in the left ear in July, 1900, and in September a discharge appeared from the ear and a little later the left side of the face appeared to be paralyzed. In October there was found suppurative otitis with a large defect in the membrane, but no tenderness over the mastoid. The forehead could be wrinkled but the left eye closed only slowly and incompletely. By the latter part of December the discharge ceased and the general condition was good. In February, 1901, he suffered some kind of injury, and headache and dizziness came on, together with increased discharge again from the ear. A few days later he became paralyzed suddenly in the right arm and the right lower extremity. In the latter part of March the paralysis was improved, but he seemed dull and complained of pain in the left side of the back of the head and also of dizziness. No choked disk. Radial artery thick and second aortic sound accentuated; pulse 80, unequal; left side of face smooth, no function of facial nerve; left lower extremity immovable; lively reflexes; both arms moved freely, grip strong, tremor; headache, frontal and occipital, drowsiness; external otitis (left). March 29 a complete mastoid resection was made, but nothing abnormal was found, and punctures of the brain did not reveal any pus. The patient became comatose after the operation and died two days later.

<sup>10</sup> Centralbl. f. Herz. u. Gefasskrankh., 1917, No. 9.

<sup>12</sup> Ziegler's Beiträge, 1899, No. 26.

<sup>13</sup> Virchow's Arch., 1920, No. 227.

At the postmortem the tibiæ were found to be thick, the skin scarred and brown; on the inner side grayish-red subperiosteal granulation tissue in small holes in the surface of the bones, otherwise is hard and thick. Skin and skeleton elsewhere showed nothing abnormal.

The heart was a little large, the aorta presented a few small yellowish spots and a small scar between the arch and the descending part.

There was bronchitis and double bronchopneumonia; bronchial nodes calcareous.

Spleen weighed 220 grams; adherent to diaphragm. Liver normal. Kidneys showed some fatty change; bladder normal; right testicle fibrous throughout and contains a yellowish-white, putty-like mass as large as a pea; in the left testicle is a yellowish-white cord containing a small concretion. Digestive tract normal.

In the left temporal fossa was a reddish-brown exudate, and under the left side of the cerebellum. The right hemisphere seemed strongly injected, reddish, while the left was pale. Along the left Sylvian artery and its branches were small yellowish-white or yellowish-gray fibrous lines and spots. Pia arachnoid adherent over the right frontal lobe; the cortex here was peculiarly reddish violet in color. Pia arachnoid over the left hemisphere was free.

The vessels at the base were greatly changed, irregularly thickened and dilated and grayish-red in color. These changes were most marked in basilar artery and in Sylvian arteries, which on the left side showed thrombosis.

Nothing abnormal was found in the left hemisphere except a small softened focus between the caudate nucleus and the internal capsule and a little larger focus in the outer part of the lenticular nucleus. The right hemisphere was hyperemic and free from other changes. There was a thin veil-like layer around the medulla and the upper part of the cord; cord and its membranes otherwise normal.

*Diagnosis.* Syphilitic endarteritis of the cerebral arteries with thrombosis in the left Sylvian artery, softening in the left caudate and lenticular nucleus; meningo-encephalitis over the right frontal lobe, the left temporal lobe and medulla; hyperemia of the right hemisphere; fibrous and caseous syphilitic orchitis; syphilitic periostitis of the tibiæ; bronchitis and bronchopneumonia.

Microscopically the walls of the arteries showed an extensive, somewhat irregularly distributed, even purely nodular inflammatory process, often with great narrowing of the lumen. The adventitia was always the seat of an extensive round-cell infiltration and also in places of connective-tissue proliferation. The media showed degeneration of the muscle cells and of the elastic layer which were broken especially the internal elastic layer underneath foci in the intima containing giant cells. The intima showed the greatest

changes: the cells had proliferated and formed compact masses which narrowed the lumen and even formed swellings of the wall. In places there was complete obliteration, oftenest due to secondary thrombosis. Giant cells, single and in masses, with peripheral nuclei and a degenerated center were found oftenest in the peripheral part of the intimal proliferation, sometimes forming tubercle-like nodules or miliary gummas. There were also foci with a great number of giant cells. A characteristic feature was numerous newly formed small vessels in the intima, and it seemed as if certain necrotic foci were due to obliteration of small vessels.

Besides the lesion in the arteries there were inflammatory changes in the membranes, more over the right hemisphere than the left, and most at the base, but present also over the medulla and the dorsal cord. The infiltration consisted of lymphocytes and some plasma cells and was directly connected with the changes in the adventitia, being often very marked around small arteries as well as veins, along which the infiltration extended into the cortex, which especially on the right side was quite hyperemic. On the inner side of the dura over the left temporal lobe was round-cell infiltration as well as fresh exudate.

This case is interesting first because of the difficulty in the way of a clinical diagnosis and next because of the extent and nature of the lesions in the brain, leptomeningeal and vascular. The endarteritis is remarkable because it occurred in the form of nodules in the region of the left Sylvian artery that often looked like aneurysms and reminded one of periarteritis nodosa. However, taking the case as a whole, there can be no question that it concerned syphilis.

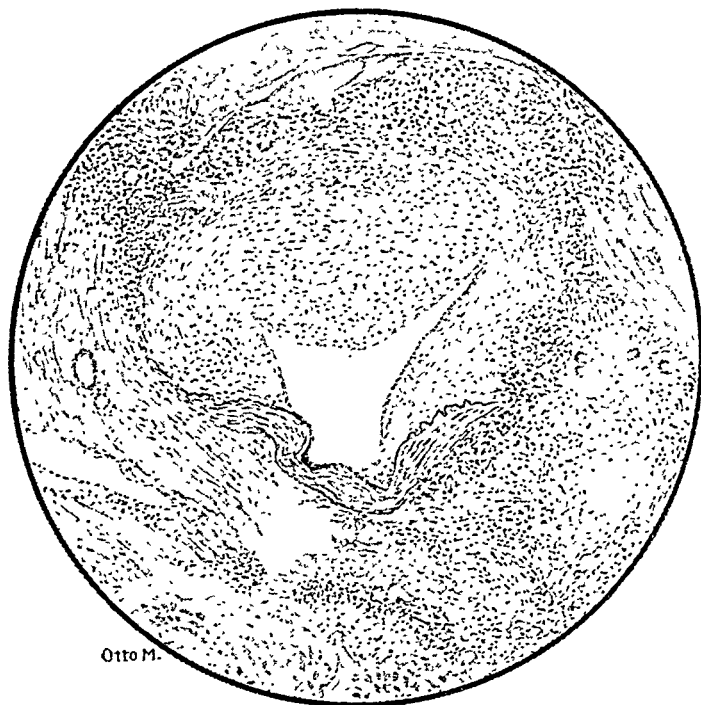
The numerous giant cells in the granulation tissue in the walls of the smaller arteries with degeneration in the intima and media place this case in a rather unusual group of gummous endarteritis. Otherwise the endarteritis seems to correspond to the usual descriptions. It is true that formerly it was denied that giant cells occur in syphilitic vasculitis, but Wright<sup>14</sup> and others have shown conclusively that they may occur.

The microscopic picture excludes periarteritis nodosa, but it brings to mind the tuberculous form of vascular lesion, but no tubercle bacilli were found—there were no tuberculous processes anywhere else—and inoculations of guinea-pigs with the caseous material from the testicle had no effect.

CASE VI.—*Syphilitic Coronary Arteritis Resembling Tuberculosis* (Figs. 7 to 9). Some years ago I<sup>15</sup> studied a case of gummous syphilis of the heart in a man, aged thirty-eight years, who had had syphilis fourteen years before and who was sick for four days

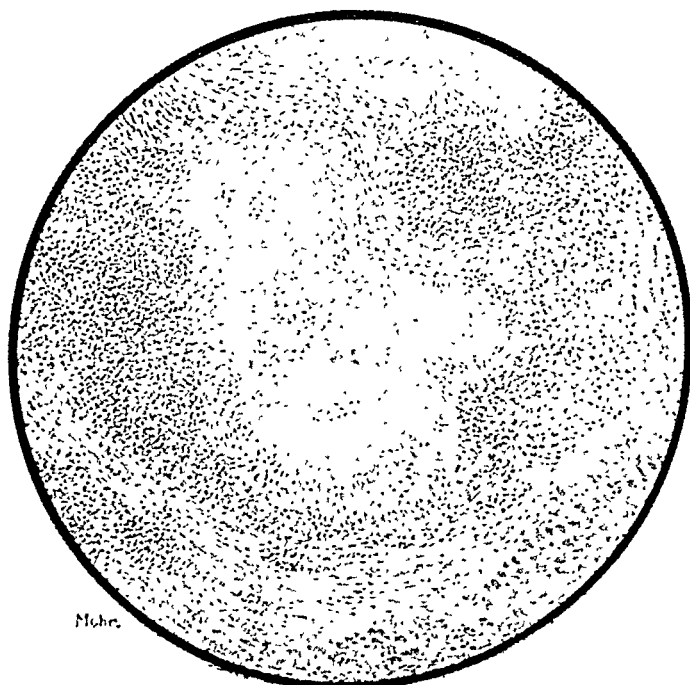
<sup>14</sup> Report of the Massachusetts General Hospital, 1903.

<sup>15</sup> Norsk. magasin f. Lægevidenskabeen, 1914.



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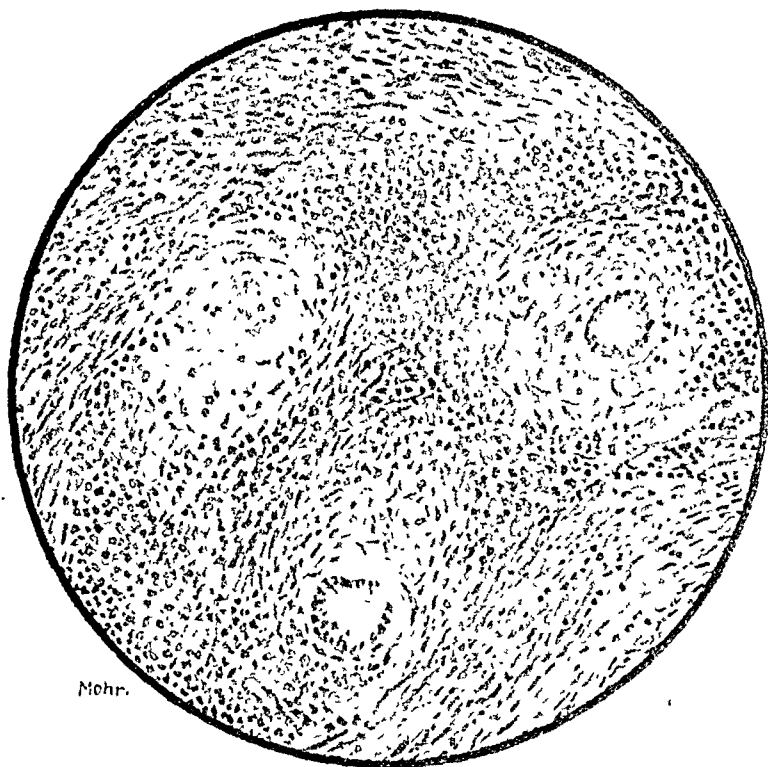
FIG. 7.—Extensive syphilitic endarteritis with necrosis and giant cells.



Mohr.

FIG. 8.—Gummatous area in the heart wall with necrosis in the center.

with dyspnea, cyanosis and rapid pulse. Gummas were found, particularly in the walls of the right ventricle and the atrium, which had resulted in obliteration of the superior vena cava. There was also a syphilitic endarteritis in the coronaries and a circumscribed gummous process in the pleura and adjacent parts of the left lung. In this case the changes in the walls of the vessels—necrosis, giant cells, etc.—resembled greatly tuberculosis, as shown by Figs. 7 to 9.<sup>16</sup>



Mohr.

FIG. 9.—Inflammatory gummatus process in the heart wall; epithelioid cells and giant cells. The appearance in Figs. 7, 8, and 9 resemble tuberculosis.

Finally, I wish to give a brief summary of a typical case of periarteritis nodosa.<sup>17</sup>

<sup>16</sup> In Norway it was early pointed out that syphilis may be the cause of important diseases in the internal organs, particularly the brain, the heart and the kidneys. Thus Gjör in 1857 described thirty cases of cerebral syphilis early in life, including cases of apoplexy, hemoplegia and general paralysis. Furthermore, E. Winge in 1863 described changes in the internal organs in syphilitics, including a case of gummous aortitis and gummas in the heart with aortic aneurysm and a case of gummous spinal pachymeningitis. But it was particularly G. Heiberg who insisted on the importance of syphilis in vascular diseases; he demonstrated in the medical society in Christiania (see *Transactions*, 1876, 1877, 1880) numerous specimens of syphilitic arteritis and aneurysms.

<sup>17</sup> *Ibid.*, 1917,



CASE VII.—*Periarteritis Nodosa* (Figs. 10 to 14). The patient was a man, aged twenty-two years, who began to suffer with stabbing pains in the left foot in April, 1916. Later he noticed that the left foot, which was tender, felt dead. It was easy for him to stumble. In the middle of May similar pains appeared in the right foot and leg and the condition in both feet became worse, at the same time as he had some fever. There was nothing of interest in the family history and the patient himself had never been seriously ill; no syphilitic infection. The cerebral nerves and the upper extremities

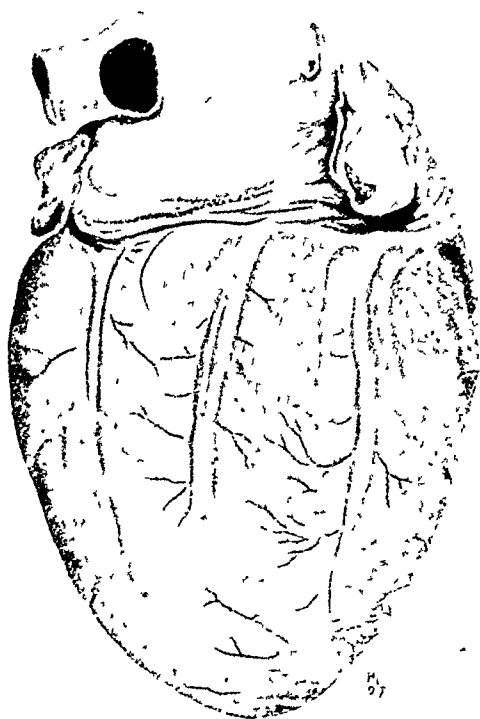


FIG 10 —Heart from the left side with numerous nodules on the small arteries

were not involved. The lower extremities were normal in position, rather thin, no tremor, no rigidity, rather weak. The muscles in the legs and thigh were tender. The walk was somewhat paretic and he could not walk on his toes or sit on his feet. Wassermann reaction negative. In November palpitation of the heart appeared; the pulse was frequent with a pressure of 160; later dyspnea appeared also systolic murmur. The urine contained albumin and casts. There was also tenderness in the epigastrium with vomiting and a slight icterus. In December edema appeared about the ankles and scrotum, also diarrhea, and the dyspnea increased, there being also

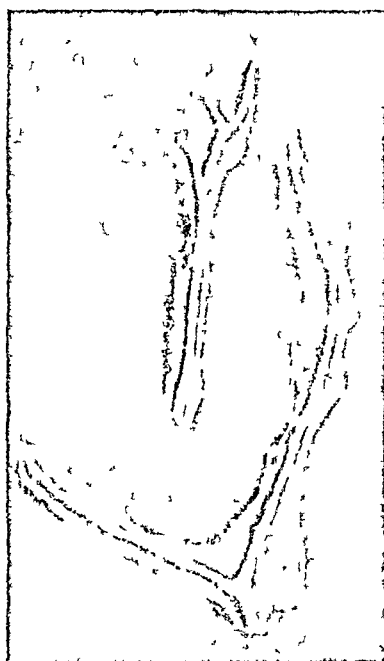


FIG. 11.—Arteries from the omentum with numerous small nodules

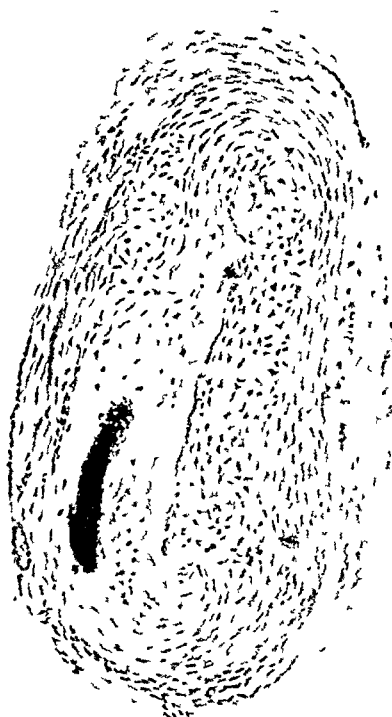


FIG. 12.—Cross-section of the coronary branch, showing infiltration of the intima with calcareous deposit, partial destruction of the media and infiltration of adventitia.

cough with bloody expectoration. The edema increased, ascites developed, the vomiting became worse and the vomited matter contained blood. Death occurred in January, 1917.

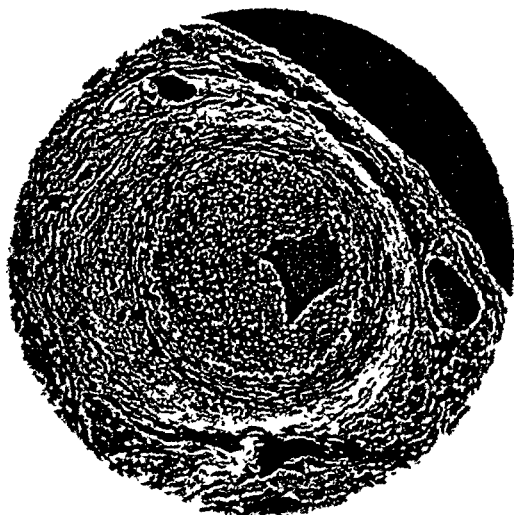


FIG. 13.—Photomicrograph of the artery in the omentum.  $\times 150$ .

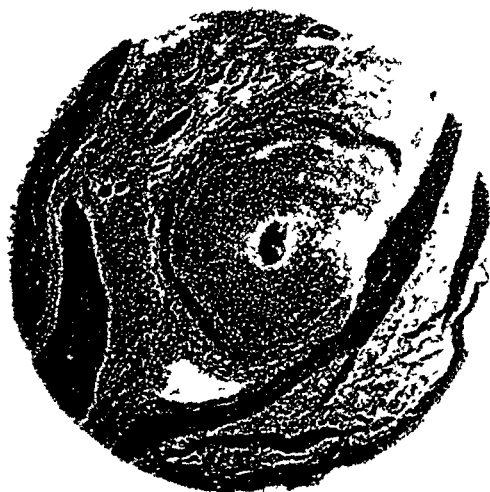


FIG. 14.—Photomicrograph of the arterial branch in the muscle of the leg.  $\times 70$ .

The postmortem examination showed altogether normal conditions in the brain and its membranes; the arteries at the base showed no changes.

The heart with 570 grams, and as shown in Fig. 10, the coronaries, which were very prominent, showed here and there oval grayish-white nodules up to the size of a hempseed, most numerous along the left side and posteriorly. In the muscles were peculiar yellowish-white spots and stripes as well as hemorrhagic infiltration, and also fibrous streaks. The heart valves were normal.

Lungs and pulmonary arteries were normal; hydrothorax. The organs of the neck and mouth were normal.

There was some ascites. The spleen contained an anemic infarct and three or four small yellowish-white spots. The liver weighed 1040 grams, fatty and passively congested. The vessels on the surface appear as white, thick strings, especially marked on the anterior surface of the right lobe.

The kidneys weighed 310 grams; on the surface numerous irregularly distributed bluish-red, slightly depressed infarct-like areas; on the surface the vessels were more prominent than usual and thicker; on the border between the cortex and the medulla are some grayish-white nodular prominences.

Adrenals and pancreas normal.

On the surface of the stomach the arteries are distinct and here and there are pinhead-sized nodules on the smaller branches. In the mucosa of the smaller curvature near the pylorus is a small ulcer and near it is a small nodule on a little arterial branch. There is a hemorrhagic erosion in the fundus. In the ileum the membrane is hemorrhagic, the follicles prominent; the large intestine showed a swollen lining with hemorrhagic infiltration and necrosis here and there.

The arteries in the omentum are nodular throughout.

The aorta is a little uneven and thick along the posterior wall; this is also true of the iliacs, but the large abdominal arteries are normal.

The spinal cord seems normal, also the vagus, phrenic, brachial, ulnar and sciatic nerves, but there was some edema and small hemorrhages in the connective tissue and muscles about the latter three nerves.

The microscopic examination of the smaller arteries in the omentum, the stomach, the heart, the kidneys and the spleen showed marked swelling of the media and intima in places, due principally to a hyaline degeneration of the connective tissue, in which were only few fibroblasts and here and there some calcareous infiltration. The change was most marked in the intima. In the media the muscle fibers and elastic layers were degenerated but not necessarily all around the lumen. The thickening led to narrowing and even complete obliteration of the lumen and also irregular nodules, so-called aneurysms, which were solid. These changes were most marked in the arteries of the heart and kidneys. In the adventitia there were only slight cellular infiltrations. Similar changes were

found in the small branches of the popliteal, in the branches of the brachial plexus and in the median and sciatic nerves with surrounding muscle tissue, and in this case there was also considerable infiltration in the connective tissue around the arteries and in the nerves, mostly of lymphocytes.

In the heart muscles was infiltration of the lymphocytes, increased in fibrous tissue, and degeneration with fragmentation of the muscle fibers with calcareous dust in places. In the kidneys degenerative and inflammatory changes as well as infarcts were present in addition to the arterial changes.

In the other organs there were no special microscopic changes other than those indicated by the naked-eye examination.

Summarizing the changes it may be noted that the smaller arteries in the heart, the kidneys, the stomach, the intestine, the omentum and in certain muscles and nerves were the seat of a productive inflammatory process, particularly in the media and intima; in the arteries in the muscles and nerves there was also an exudative process, particularly in the adventitia.

Periarteritis nodosa presents different clinical forms according as different organs are involved. It begins usually acutely in previously well persons and attacks mostly young and strong men between twenty and forty years of age, the first symptoms as in this case being indefinite pains in the muscles of the trunk as well as of the extremities and in the joints with fever; there may be edema and changes in the skin with disturbances in sensibility, paresis, exhaustion and weakness, the pulse often being very frequent and irregular. Death usually occurs after some weeks up to six or eight months after increasing weakness, dyspnea, renal and digestive disturbances as well as cardiac troubles. Death has been observed as early as ten days from the beginning and as late as after one or two years. The most common form is the muscle-nerve type, to which the case I have described belongs. In other cases the principal symptom may be renal or gastro-intestinal or cardiac; other organs, *e. g.*, the skin, may be especially involved, but as before stated the brain is rarely affected. The disease appears to be curable—four such cases have been described—and it may well be that more instances of recovery of mild or abortive forms will be recognized as the disease becomes better known. Most of the cases—between sixty and seventy in all—have been described in German literature and only remarkably few in the English and American.

The primary anatomical changes are in the small and medium-sized arteries in the heart, kidneys, digestive tract, etc., where they give rise to the very characteristic oval grayish-white, usually firm aneurysm-like nodules in linear arrangement on the small arteries. The lumen is usually narrowed, but true aneurysms have been observed. The large arteries, as a rule, are not involved. The narrowing and thrombosis of the arteries form the basis for the

other anatomical changes as well as the clinical phenomena; necroses and degenerations, hemorrhages and hemorrhagic infiltrations.

Microscopically the inflammatory changes in the arteries appear to be infectious. There is no agreement as to whether the changes develop first in the media or adventitia, although many believe that the media is first involved, fibrinous exudation and edema with degenerative and necrotic changes in the muscle fibers and elastic tissue, together with round-cell infiltration preceding the formation of connective tissue. By some the primary lesion is believed to be a periarteritis which extends into the media and involves the intima in proliferation. When the changes are acute true aneurysms may form.

Such in brief appears this disease of the arteries. It has many things in common with the so-called syphilitic endarteritis, but there are also differences. As emphasized by Guldner,<sup>18</sup> the presence of spirochete and a positive Wassermann reaction would establish the diagnosis of syphilis, which frequently involves the cerebral arteries while periarteritis nodosa rarely occurs in the brain; in syphilis the intima is first involved, whereas in periarteritis the media or the adventitia; in syphilis gummatous changes and giant-cell formation occur while the latter is rare in periarteritis nodosa; and finally in the syphilitic endarteritis the elastic membranes are split apart and new elastic tissue may be formed, but there is no such fracturing of the elastic layers as in periarteritis. Spiro<sup>19</sup> points out that the infiltration in periarteritis regularly contains polymorphonuclear leukocytes, which are absent in syphilitic endarteritis, and the vessel wall is attacked only partially in periarteritis, whereas in syphilis the process usually extends all around the vessel. It should be noted that in syphilitic endarteritis the intima may be attacked secondarily; that the giant-cell formation is rather unusual in both these forms of arterial disease, although more so in periarteritis nodosa; and the necrosis in periarteritis nodosa may be quite considerable even though large gummatous areas do not form. There seems to be no absolutely distinctive difference between these two diseases of the arteries, and consequently it is not difficult to understand that they may be confused. Versé<sup>20</sup> has advanced the opinion that they may be identical because they have so many things in common; thus aneurysms may develop in syphilitic endarteritis and necroses are present in both processes as well as giant-cell formation, and he suggests that periarteritis nodosa may be a special form of arterial syphilis affecting small and medium-sized arteries—but if only a few of the cases of periarteritis nodosa has syphilitic infection been definitely demonstrated and, as a rule there is no history of syphilis and the Wassermann

<sup>18</sup> Virchow's Arch., 1915, No. 219.

<sup>19</sup> Ibid., 1920, No. 227.

<sup>20</sup> Ziegler's Beiträge, 1907, No. 40.

reaction is negative. While it is true that the lesions in these two diseases in many respects corresponds in particular details, the complete anatomical picture seems to me to indicate that it concerns two distinct diseases.

Certain writers hold that periarteritis nodosa is not a distinct entity because no specific virus as yet has been demonstrated and because various pyogenic microbes have been found in some of the cases (staphylococci, streptococci;) it is also pointed out that preceding infections such as angina, typhoid fever, diphtheria and acute rheumatism may be regarded as predisposing, in some cases at least, to the development of periarteritis nodosa. It is true, as discussed in the earlier part of this article, that arteritis occurs in different forms of infection, but at present the view that the disease is not specific may be regarded as merely hypothetical. To me it seems most reasonable to regard periarteritis nodosa as a definite disease due to a distinct virus. While the clinical picture may be variable, depending on the distribution of the lesions of the arteries, the lesion itself is quite characteristic enough to warrant the belief that it concerns a specific disease. Recently, v. Haun<sup>21</sup> by inoculation of the blood of a patient with periarteritis nodosa claims to have produced the disease in guinea-pigs, but of course further investigation is required.

In conclusion I would point out that forms of true arteritis occur more frequently than usually believed, that they apparently differ etiologically, and that they present anatomical appearances that make the differential diagnosis difficult, this being particularly true of the vascular changes in syphilis, periarteritis nodosa and also in tuberculosis.

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## POSTOPERATIVE DIETOTHERAPY.<sup>1</sup>

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PRIOR to the middle of the nineteenth century the dietetic treatment of most acute disease conditions consisted in virtual starvation. Graves, in 1848, first insisted that a fever patient should be fed. Today clinicians are in accord regarding the dietary treatment of febrile conditions. The high calorie treatment of typhoid fever is a

<sup>21</sup> Virchow's Arch., 1920, No. 227.

<sup>1</sup> Read before the Richmond Academy of Medicine, Richmond, Va., February 22, 1921.

more recent development, but its value has been demonstrated beyond cavil. Many a case so treated has on convalescence weighed as much as he had before the onset of his illness, and the frequency of complications has been diminished. In the treatment of lobar pneumonia little attention was formerly paid to dietary regimen. This is a limited disease, usually of one week or of ten days' duration. Physicians believed that for this period the patient could do well on any diet, provided it was light enough, and as a result it usually consisted in liquids of low food value. But pneumonia often, by developing complications, becomes a protracted disease. In this case the diet becomes most important, and those individuals who have been practically starved throughout the first week must continue the fight at a handicap. In the more modern treatment every pneumonia patient is considered as potentially a chronic, wasting case.

The surgeon notoriously pays less attention to dietary treatment than does the internist. In many surgical clinics postoperative treatment still consists in partial starvation. The desire to prevent nausea and vomiting results in undue caution. We do not imply that an individual whose stomach is upset should be fed, but would emphasize that food should not be withheld for several days after the acute gastric symptoms have subsided. A certain number of surgical cases develop complications requiring prolonged treatment. Just as in pneumonia it is essential that every case be treated as potentially of long duration. No harm will be done to those who recover rapidly, and the precaution may be life-saving to those who are so unfortunate as to develop untoward sequelæ.

It is our intention to discuss in this paper only the general dietary management of postoperative cases without reference to those instances in which the presence of complicating medical conditions or operations on digestive organs call for special methods. The latter group is of great importance and merits intensive discussion, but time permits reference only to general dietary principles in surgery.

The treatment of operative cases begins before operation. It is frequently advisable to keep the patient in bed for some days prior to operation, in order to build up the general resistance. A light, highly nourishing diet relatively rich in carbohydrates may be given up through the day preceding operation.

The importance of a liberal fluid intake before operation cannot be overemphasized. Recent studies in the causation of shock bring out the important role played by the fluid content of the blood. The symptoms of shock are due to a deficient amount of circulating fluid in the bloodvessels. In mildly shocked individuals this deficiency follows a draining of blood into abnormally dilated capillary beds, while in severe shock there is added a loss of fluid by transudation out of the vessels into the tissues, due to an abnormal per-



meability of damaged capillary endothelium. The prevention of shock depends in part at least on the maintenance of a normal blood volume. The practice still occasionally in vogue of withholding fluids for some hours previous to operation results in preliminary dehydration and renders the body less able to combat shock when it occurs.

Following operation the patient usually receives nothing by mouth during the first twenty-four hours. During this period the stomach is usually upset and there is a strong tendency to nausea and vomiting. If these symptoms are absent there is no reason for protracted withholding of food. The administration of fairly abundant fluids before operation frequently lessens the tendency to nausea and vomiting. Another precaution which is frequently successful is that of washing out the stomach while the patient is still under the influence of the anesthetic. As soon as the stomach will tolerate ingested material fluids may be administered. It is best first to try out the patient with water or with weak tea, or if stimulation is necessary, strong coffee. Usually by the second day the patient is in condition to take liquid nourishment. Sometimes this occurs sooner.

The liquid dietary used in most surgical clinics, and also in many even of the more progressive medical clinics, is based upon two essential food substances: milk and raw eggs in the form of egg-white, albumen water or eggnog. Milk is frequently contraindicated in postoperative conditions because of the tendency to distention, and therefore albumen water is often the chief constituent of liquid diets. Scarcely any food substance is less fitted to be the principal article of diet than is uncooked egg-white.

The popularity of this article in treatment arose from the classical work of Beaumont, who found that raw egg-white left the stomach more rapidly than did any other food, and concluded that it was more rapidly digested. Little attention has been paid to more recent work demonstrating that this rapid emptying occurs because raw egg-white is not digested at all in the stomach.

Bateman has summarized the evidence in support of this statement. The outstanding facts are as follows: Raw egg-white has but feeble ability to stimulate the flow of gastric juice. It is actually no more powerful than a similar amount of water. Cooked egg-white, on the contrary, causes the production of an abundant gastric secretion and unites rapidly with the hydrochloric acid. The raw untreated substance possesses an antibody which resists the action of pepsin. Not only is it resistant to digestion in the stomach, but it has also an antitryptic action. It calls forth no increased secretion of bile. After having passed the stomach it is but poorly digested in the intestines. Native egg-white when fed with other easily digestible proteins prevents the digestion and absorption of the latter. This has been proved by numerous investigators. Bate-

man suggests as an explanation that the colloidal egg-white absorbs the trypsin, thus diminishing its activity in much the same way as does charcoal.

Administered by mouth, raw egg-white produces diarrhea and sometimes vomiting in dogs. This has been produced by as small an amount as the whites of two eggs. Diarrhea has also been produced in numerous cases in man even after as small a quantity as the whites of four eggs. Mendel and Louis have shown that after the ingestion of small amounts of native egg-white the latter could be recovered unchanged from the stools. In experimental work it made little difference whether the raw-food was eaten alone or with other foods. In the latter case diarrhea was later in appearing. Substances added to the diet which stimulate the flow of gastric juice do not aid in the digestion of egg-white. In man from 30 to 50 per cent of egg-white is completely lost as such in the feces.

Cooked egg-white produces none of these symptoms, and when fed even in large amounts 90 per cent of it is utilized. It is only necessary to produce coagulation. Coagulation is complete with a resultant jelly-like mixture if the temperature is raised to 70°. Heating to a higher point and cooking more thoroughly in no way impairs the digestibility.

Experiments on man consisting of the feeding of raw egg or egg-white produced, as a rule, either diarrhea or flatulence, or both. This sometimes occurred with as small an amount as the whites of four eggs daily. The beating of eggs into a froth made little difference in the result.

Hamburger and Cramer claim that albuminuria follows the ingestion by man of large amounts of beaten egg-white. Stokvis believes that raw egg-white taken in quantity is absorbed and undigested and excreted in the urine, thereby damaging the renal epithelium. Quite recently Van Alstyne has shown that raw egg-white taken into the alimentary tract may enter the circulation and be excreted through the urine.

In spite of the foregoing facts one may find on perusal of current books on dietetics that raw egg-white is still extensively recommended as an excellent nourishing food for invalids.

We may sum up the case against uncooked egg albumen in saying: (1) That it is very poorly digested and absorbed; (2) that as high as 50 per cent is lost in the feces; (3) that it tends to produce gastrointestinal upsets; (4) that at times it appears to produce an albuminuria, a condition certainly not to be desired in postoperative cases in which the kidneys already are overworked, as evidenced by the frequency of albuminuria following general anesthetization. All of these disadvantages are eliminated by the simple process of coagulation.

While egg-white is principally protein the preponderating element in the food of postoperative cases should be carbohydrate. During

operation the metabolism is usually increased and the reserve supply of carbohydrate in the body is to some extent depleted. Carbohydrate should now be administered to furnish additional energy and to protect the patient's own body protein. If protein alone is given the basal metabolism increases as a result of the specific dynamic action of protein. Protein so stimulates the metabolism that the rate of heat formation in the body is accelerated. Sugars and fats have a similar dynamic action, but to a much less marked degree.

Most patients after undergoing an operation and postoperative treatment leave the hospital weighing decidedly less than upon entry. It seems reasonable to hope that under proper dietary care these patients may do equally well as those treated by high calorie, high carbohydrate diets in typhoid fever, and that individuals may leave the hospitals weighing as much as or more than upon entrance. If this is to be attained it can best be done by feeding diets of relatively high caloric value and relatively high in carbohydrates.

It is nevertheless essential that sufficient protein be administered to repair the waste and loss of protein from the body tissues. Chittenden has shown that with slightly less than 1 gram of protein per kilogram of body weight the amino-acid requirements of the tissues will be safely met. The average adult individual weighs about 70 kilograms. With 1 gram of protein necessary per kilogram of body weight the daily diet should then contain approximately 70 grams of protein. This will contribute about 280 calories to the daily requirement, and we must rely upon carbohydrates and fat for the balance. It makes little difference which of these two latter substances preponderates as long as the fat does not furnish more than 90 per cent of the non-protein calories. In view of the tendency to acidosis in postoperative cases, as indicated by the presence of acetone in the urine, it would appear more rational to utilize carbohydrates in preference to fats.

To return to a discussion of the protein it is important to note that recent researches have shown that different proteins vary greatly in their ability to maintain nitrogenous equilibrium. This is because certain ones, such as those from cereals, are deficient in one or more of the essential amino-acids. Van Slyke remarks that a man who might be kept in equilibrium on 4 grams of nitrogen per day in the form of beef, milk or eggs would require 8 grams as bread or potatoes and 16 grams as beans. Thus it would appear advisable when we are giving proteins to give those of higher value, such as meat or meat derivatives, milk, eggs and fish. We must differentiate between proteins of good quality and those of poor quality.

It is not enough that a diet possesses sufficient calories and is composed of the right proportion of foodstuffs. Sufficient vitamins must be present. The food must be palatable. There must be sufficient variation so that the diet will not become irksome. The food must be so prepared that it is easily digested and absorbed.

The physical texture and the fineness of division are factors worthy of consideration. In general the more finely divided the food the more rapidly does the digestive juice penetrate and the more rapidly does digestion take place. Indigestible solids not only act as stimulants to peristalsis but apparently actually retard normal absorption. The method of cooking is important. Fried substances are covered by a layer of material which the gastric juice can neither readily dissolve nor penetrate.

If the diet contains a fairly abundant proportion of milk and of eggs whose albumen has been coagulated there is little danger of deficiency in vitamins, either in the fat-soluble A or in the water-soluble B.

## DIET NO. I.—FEEDINGS EVERY TWO HOURS.

Time.	Amount.	Protein, grams.	Fat, grams.	Carbo- hydrate, grams.	Calories.
7 a.m. Hot milk	200 cc	6.6	8.0	10.0	138.40
9 a.m. Oatmeal gruel	100 cc				
With milk	100 cc	4.5	4.4	11.3	102.80
Coffee with cream	25 cc				
With cane sugar	8 gm.	0.55	10.0	8.75	127.2
11 a.m. Orange juice	50 cc				
Lemon juice	25 cc				
Lactose	50 gm.				
Water	150 cc	0.4	0.1	58.25	235.5
1 p.m. Chicken broth	150 cc	5.4	0.5	2.25	35.10
Cocoa	5 gm.				
With lactose	30 gm.				
With cream	50 cc				
With milk	100 cc	5.48	25.44	38.38	404.40
3 p.m. Buttermilk	200 cc	6.0	1.0	9.58	71.32
5 p.m. Grape juice	125 cc				
With lactose	25 gm.	.....	.....	31.25	125.00
7 p.m. Cream of tomato soup	150 cc	10.65	42.64	41.05	590.56
Soft-cooked egg	50 gm.	5.95	4.65	.....	65.55
9 p.m. Hot milk	150 cc	4.95	6.0	7.50	103.80
		50.48	102.93	212.06	1999.73

Time.	From the kitchen.	Amount.	From the floor.	Amount.
7 a.m.	.....	.....	Hot milk	1 glass.
9 a.m.	Oatmeal gruel with milk	1 serving		
	Coffee with cream and sugar	1 cup		
11 a.m.	.....	.....	Orangade with lactose	1 glass.
1 p.m.	Chicken broth	1 bowl		
3 p.m.	.....	.....	Buttermilk	1 glass.
5 p.m.	Cream soup	1 bowl		
	Soft-cooked egg	1 egg		
7 p.m.	.....	.....	Grape juice with lactose.	1 glass.
9 p.m.	.....	.....	Hot milk	1 cup.

Palatability depends (1) on variation and (2) on the type of food administered. Only two food substances are naturally appetizing and do not require seasoning. These are animal foods and fruits. The use of fruit juices for increasing palatability is well known. The addition of meat extracts for the same purpose may be employed.

The accompanying tables are examples of postoperative dietaries in use at St. Elizabeth's Hospital, Richmond, Va. They are made up on a basis of 2000 calories with a protein intake slightly below 1 gram per kilogram of average body weight. It has been amply demonstrated by various workers, and particularly in reports from the Nutrition Laboratory of Copenhagen, that for limited periods

DIET NO. II.—FEEDINGS EVERY TWO HOURS.

Time.		Amount.	Protein, grams.	Fat, grams.	Carbohy- drate, grams.	Calories.
7 a.m.	Chicken broth	100 cc	3.6	0.1	1.5	21.30
9 a.m.	Soft-cooked egg	50 gm.	5.95	4.65	....	65.65
	Oatmeal gruel	100 cc	1.2	0.4	6.3	33.60
	Coffee with cream and sugar (cane)	25 cc 8 gm.	0.55	10.0	8.75	127.20
11 a.m.	Grape juice	150 cc	....	....	37.50	150.0
1 p.m.	Cream of green pea soup	200 cc	15.56	56.88	88.04	806.32
	Orange juice	50 cc				
	With lemon juice	25 cc				
	With lactose	50 gm.				
	With water	150 cc	0.4	0.4	58.25	235.80
3 p.m.	Beef juice	100 cc	4.90	0.60	....	25.0
5 p.m.	Malted milk	12 gm.				
	With cocoa	5 gm.				
	With lactose	25 gm.	4.13	4.30	4.01	191.26
	Soft poached egg	50 gm.	5.95	4.65	....	65.65
7 p.m.	Boiled custard	100 gm.	6.27	6.32	31.35	207.36
9 p.m.	Barley water	200 cc	0.52	0.11	3.64	17.63
			49.03	88.11	239.34	1946.47

Time.	From the kitchen.	Amount.	From the floor.	Amount.
7 a.m.	.....	.....	Chicken broth	1 cup.
9 a.m.	Oatmeal gruel	1 serving		
	Soft-cooked egg	1 egg		
	Coffee with sugar and cream	1 cup		
11 a.m.	.....	.....	Grape juice	1 glass.
1 p.m.	Cream soup	1 bowl		
	Orangeade	1 glass		
3 p.m.	.....	.....	Beef juice	1 cup.
5 p.m.	Chocolate malted milk	1 glass		
	Soft poached egg	1 egg		
7 p.m.	Boiled custard	1 cup		
9 p.m.	.....	.....	Barley water	1 cup.

of time the reduction of protein intake to as low as 29 grams per day is without deleterious effects. This is particularly true if the proteins are of "good quality" and if the patient is at rest in bed. The caloric intake is slightly in excess of that usually estimated as required by an individual at rest in bed and therefore provides for a slight gain in weight. The diets are all relatively high in carbohydrates.

## DIET NO. III.—FEEDINGS EVERY TWO HOURS.

Time.	Amount.	Protein, grams.	Fat, grams	Carbo- date, grams.	Calories.
7 a.m. Orange juice	100 cc	0.8	0.2	28.07	117.28
Lemon juice	15 cc				
Lactose	15 gm.				
9 a.m. Cream toast	30 gm.				
With milk	100 cc				
With butter	1 oz.				
With flour	1 oz.	7.78	12.49	7.45	173.33
Poached egg	50 gm.	5.95	4.65	....	65.65
11 a.m. Chicken broth	100 cc				
With cracker	10 gm.	4.58	1.01	8.81	62.65
1 p.m. Cream of pea soup	200 cc	15.56	56.88	58.04	806.35
3 p.m. Oatmeal gruel with milk	100 cc	8.72	8.10	21.83	195.10
5 p.m. Poached egg on toast	20 gm.	7.87	13.39	10.54	194.15
Butter	10 cc				
7 p.m. Baked custard	100 gm.	7.60	6.65	12.50	140.25
9 p.m. Malted milk	12 gm.				
With cocoa	5 gm.				
With lactose	25 gm.	10.39	11.56	48.07	237.88
		69.25	114.93	195.93	2092.81

Time.	From the kitchen.	Amount.	From the floor.	Amount.
7 a.m.	.....	.....	Orangeade with lactose	1 glass.
9 a.m.	Cream toast	1 serving		
	Poached egg	1 egg		
11 a.m.	.....	.....	Chicken broth with cracker	1 glass.
1 p.m.	Cream soup	1 bowl		
3 p.m.	Oatmeal gruel with milk	1 serving		
5 p.m.	Poached egg on toast with butter	1 serving		
7 p.m.	Baked custard	1 serving		
9 p.m.	.....	.....	Chocolate malted milk	1 glass.

Diet No. I is usually the first administered and should be given as soon after operation as the patient's condition safely permits. It corresponds to the so-called liquid diet, although there are included in it such non-liquids as strained oatmeal gruel and a

soft-cooked egg. Diet No. II is used interchangeably with the former and is particularly useful in those cases with milk intolerance or with a tendency to abdominal distention. Diet No. III follows Diet No. I or No. II usually by about two days. When it is found that the patient tolerates the first diet well he may rapidly be changed to the third. In this the feedings are alternated, liquid and semisolid. After an additional day or two, or as long as is necessary in each individual case, Diet No. IV is given, consisting of semisolid food.

#### DIET NO. IV.—FEEDINGS EVERY TWO HOURS.

Time.		Amount.	Protein, grams.	Fat, grams.	Carbo- hydrate, grams.	Calories.
7 a.m.	Baked apple	120 cc	0.61	0.58	29.30	124.86
9 a.m.	Wheat farina	100 cc				
	With milk	100 cc				
	With lactose	15 gm.	14.50	5.40	96.30	491.0
	Toast with milk	100 cc				
	Toast	40 gm.	7.12	12.54	7.10	169.74
11 a.m.	Plain junket	100 gm.	3.30	4.0	19.67	127.88
1 p.m.	Creamed fish	50 gm.	17.48	18.83	26.24	344.35
	With white sauce	100 cc				
	Purée of spinach	100 gm.	2.10	4.10	2.60	55.70
3 p.m.	Apricot souffle	.....	6.37	21.56	17.85	290.92
5 p.m.	Chicken broth	100 cc				
	With rice	50 gm.	5.0	0.60	1.50	31.40
	Poached egg	50 gm.				
	On toast	20 gm.				
	With butter	10 cc	7.87	13.39	10.54	194.15
7 p.m.	Stewed prunes	100 gm.	0.50	0.10	22.30	92.10
9 p.m.	Barley gruel with milk	120 gm.	5.94	6.41	13.25	134.45
			70.59	87.51	246.65	2056.55

Time.	From the kitchen.	Amount.	From the floor.	Amount.
7 a.m.	Baked apple	1 large		
9 a.m.	Wheat farina with sugar and milk	1 serving		
	Milk toast	1 serving		
11 a.m.	Plain junket	1 cup		
1 p.m.	Creamed fish	1 serving		
	Purée of spinach	1 serving		
3 p.m.	Apricot souffle	1 serving		
5 p.m.	Chicken broth with rice	1 bowl		
7 p.m.	Stewed fruit	1 serving		
9 p.m.	Barley gruel with milk	1 serving		

The feedings in all four diets are administered every two hours. The directions to the nurse are simplified as shown in the accom-

panying tables, which indicate the amount to be given and whether it is to come from the kitchen or is to be made up by the nurse in the ward.

The advantages of these four groups of diets are as follows: (1) A graduated increase in feedings is provided for each uncomplicated case; (2) the diets are composed of the proper proportions of protein, fat and carbohydrate; (3) the nourishing value is high; (4) all diets are sufficiently varied and are palatable.

In practical experience we have found the diets to be satisfactory. No striking advantage over the usual method of feeding is to be seen in the average postoperative case. It is particularly in those cases which develop untoward complications with prolonged convalescence that the comparative advantages become apparent. Nevertheless, we have observed that patients placed on these dietaries are much more content than others treated by the usual method. This paper is in the nature of a preliminary report and will be followed by a comprehensive comparison of the results from the two methods, a comparison of the weight curves and a discussion of the influence on postoperative conditions such as albuminuria and acetonuria.

We would particularly emphasize that in postoperative treatment the diet must be individualized. Every patient is a law unto himself. The patient's likes and dislikes should always be consulted and agreeable food substituted for that which is distasteful. This can easily be arranged in our diet. The dietaries above described will be relished by the majority of individuals, but when necessary substitution should be freely employed provided care is taken not to change the relative proportion of protein, fat and carbohydrate and not to alter markedly the caloric value.

Mendel has said: "Unfortunately, rational dietetics founded upon the newer knowledge of the chemistry of foods and nutrition has not yet received the discriminating study and advocacy on the part of practical clinicians that its importance unquestionably warrants." This paper is a plea for the rational application to practical medicine and surgery of the more recently demonstrated scientific facts in physiology and biochemistry and for the elimination of those principles which have already been proved to be in error.

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## ADDISON'S DISEASE: A CASE OF TUBERCULOSIS OF THE ADRENALS.

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THE purpose of this paper is to report a case of Addison's disease, including the case history and autopsy findings. The writer is indebted to Dr. J. W. Bruner and Dr. A. C. Morgan for permission to report the case and the use of the clinical report.

During previous experience in postmortem work several cases of Addison's disease have been encountered, two of which stand out prominently. One had been considered a clinical case of Addison's disease and had been used for teaching purposes. At autopsy no lesions whatsoever of the adrenal could be demonstrated. The second case had not been diagnosed and presumably had not shown the clinical features, while at autopsy large tuberculous adrenals were found.

The present case was diagnosed clinically, presenting the classical symptoms, while at autopsy definite tuberculosis of the adrenals was demonstrated. The following clinical history obtained by Dr. Morgan presents the typical signs and symptoms of this disease:

Mr. G. S., aged forty-three years, principal of a high school.

*Chief Complaint.* October 30, 1920, the patient complained of a very tired feeling which has increased during the past six weeks.

*Past Medical History.* In November, 1918, he was sick for one week succeeding the influenza epidemic. He has had numerous attacks of tonsillitis until the removal of the tonsils four years ago. Had the usual diseases of childhood. The patient has had an active life working on a farm until twenty-five years old, when he attended the Bloomsburg Normal School and has been teaching ever since. During the summer of 1918, in Maryland, he had an attack of illness of a week in which he complained of being very tired and dizzy, but no pain. He had never had chills, but has been subject to bleeding gums for some time.

*Social History.* Married for the past eighteen years, but has no children. Wife never pregnant. His heaviest weight was 175 pounds twenty years ago. Average weight, 154 to 164 pounds, and about a month ago this dropped to 151½ pounds. His appetite has been good until the past week. He has been subject to bilious attacks for several years. This has been accompanied by nausea and occasional vomiting lasting for two days. This has occurred

as often as once a week, but lately about every six months. These attacks were relieved by laxatives.

*History of Present Illness.* The school term of 1919-20 seemed to leave the patient a little more tired than usual. He spent the summer months at Danville, Pa., caring for his father, who died at the age of seventy-seven years. At this time the patient lost considerable sleep and was under great strain. The patient returned to his school duties, and about September 15 noticed that he became extremely tired upon the least exertion. Work seemed to pile up, his strength lessened and he fell back considerably. The patient did not worry over this and had a clerk to aid him. During the past week the weakness seemed to have progressed considerably. The illness is not associated with pain, and walking short distances is accomplished without effort. Standing still causes dizziness and faintness and the patient must sit down to get relief.

*Physical Examination.* Face and neck are very dark, edging off at the clavicles. At times they are ashen gray. The lips are dusky and pigmented, but not the appearance of cyanosis. The gums are very much pigmented and resemble those of a bull dog. Both nipples show marked deep brown pigmentation, with well-marked lines of demarcation. No pigmentation over the axillæ or pubes. The hands show a tendency to pigmentation, but not to the same extent as does the face. From the wrist to above the elbow the discoloration is apparently due to ordinary exposure effects. The heart outline seems smaller than normal on percussion. No adventitious sounds. The lower border of the stomach is on a level with the umbilicus. The liver is five inches in depth in the right nipple line. The spleen seems increased on percussion in the left axillary line. On deep palpation under the left costal margin there is decided tenderness and apparent resistance down to the level of the umbilicus, but no distinct mass is felt. Bimanual palpation of both flanks gives some tenderness, but without definite localization. The feel of the muscles is very flabby.

*Urine Analysis.* (a) Amber; clear; acid; 1016; negative for albumin, sugar and indican; long, narrow hyaline casts; occasional leukocytes, epithelium and urates.

(b) 1020; acid; very faint trace of albumin; indican plus; no acetone, diacetic acid or sugar; urea, 10.56 grams per 960 cc; epithelial cells; hyaline casts (1); bacteria; amorphous urates.

(c) 1010; very faint trace of albumin; 1 hyaline and 1 granular cast; epithelial cells and bacteria.

*Blood Examination.* Red blood cells, 3,840,000; white blood cells, 10,200; hemoglobin, 90, Cl, 1; polynuclears, 45; large lymphocytes, 30; small lymphocytes, 32; eosinophils, 3; microcytes; macrocytes; poikilocytosis. Cells have tremendous ameboid motion. Cannot find malarial parasites in stained specimen.

*Blood-pressure.* Systolic, 84; diastolic, 58; pulse-pressure, 94; regular tones very soft and without murmur.

*Renal Function.* December 7, 1920. Reaction time, fifteen and one half minutes. Percentage in first specimen, 15; second, 10; total, 25. CO<sub>2</sub> in alveolar air, 40 per cent.

*Blood Examination.* December 3. Red blood cells, 3,690,000; white blood cells, 7,200; hemoglobin, 85 per cent; polynuclears, 72; small lymphocytes, 24; large lymphocytes, 2; neutrophils, 2.

*Examination of the Chest, Roentgen Ray.* Peribronchial markings are well-defined throughout both lungs. The right upper lobe extending from the apex to the first interspace anteriorly shows a definite tuberculous infiltration. The left apex shows a similar condition with several dense small calcified tubercles. The appearance of the condition of the right apex would suggest a more recent activity. Examination of the sinuses show the frontal sinuses quite large, but no evidence of any infection.

*Examination of the Teeth.* Subject to bleeding gums for some years. Examination shows no evidence of infection of the upper jaw. The lower right anterior bicuspid, which has been crowned, shows a pericementitis with apical infection.

The autopsy was made at the patient's residence through the courtesy of Dr. J. W. Bruner, and the following is the report:

Date of death, January 14, 1921.

Date of autopsy, January 14, 1921, 8 P.M.

*Clinical Diagnosis.* Addison's disease.

*Cause of Death.* Bilateral tuberculosis of the adrenals.

*Associated Diagnosis.* Acute pulmonary hypostatic congestion, bilateral. Cardiac dilatation. Chronic degenerative nephritis with pyramidal anemia. Arrested pulmonary apical tuberculosis.

*Gross Description.* The body was that of an adult white male, forty-three years of age, moderately well nourished, slight *livor mortis* in the dependent positions and rigor moderately marked eight hours after death. The face and exposed parts of the neck, the hands and lower arms had a dark bronzed color, due apparently to a pigmentation which had diffused and evenly distributed in the cutaneous layer. It was observed that this bronzed color was very much less marked after than before death. The pigmentation did not involve the covered portion of the body, although in these there was a pasty pallor.

The usual primary incision was made from the episternal notch to the symphysis pubis, and the breast plate was removed.

*Chest.* There was no fluid on either side; the lungs were partially collapsed. At both apices old pleural fibrous adhesions attached the lung to the parietal wall firmly enough on the right side to tear the lung structure during removal.

The right lung, in the uppermost portions, was pallid, soft and crepitant, with moderate lines of anthracotic markings. The dependent position, especially of the lower lobe, was darker blue in color, boggy to palpation and a considerable amount of frothy

blood-tinged fluid exuded from the cut surface. There was no evidence of consolidation. The apex of the upper lobe was torn in removal, considerably reacted by scar tissue, contained several well-circumscribed and densely fibrotic nodules which presented upon section caseous centers.

The left lung was a counterpart of the right, with the exception that the nodular involvement at the apex, while present, was less marked. This was an old process and there was no evidence of a recent flare-up.

The pericardium contained the usual amount of serous fluid, and there were no adhesions.

The heart, *in situ*, was dilated and the large vessels on the venous side were dilated and filled with blood. This dilatation involved the right auricle. The coronary vessels were partially dilated with no evidence of fibrosis.

The thymus gland showed distinctly its outline and was removed without much difficulty. Upon section the structure was somewhat dense by reason of a fibrosis, but the replacement by fat predominated. At the upper positions of the thymus and upon both sides of the vessels several large masses of darkly pigmented lymph nodes were found. There was no other involvement of lymph nodes in the neck.

The thyroid was not enlarged and its gross appearance was that of the normal pink, fleshy color and character.

*Abdomen.* The abdomen was flat. The omentum was thick and well nourished. This tendency to the deposition of fat was also noticed in the subcutaneous areas here at the expense of muscular development.

The usual anatomy of the abdominal cavity was preserved; the appendix was normal and the gall-bladder slightly distended, but free from adhesions. The lower border of the liver had the usual outline, being at the costal margin. The liver was a dark, slaty color with a tendency to swelling of the parenchyma. The bile ducts were patulous and free from stones.

The spleen was slightly enlarged, of a slaty gray color, and upon section the splenic pulp was dark blue with the follicles standing out distinctly.

*Suprarenals.* Both organs were involved in exactly the same manner and the process was sharply confined to the suprarenal bodies. There had been no extension from within outward and no evidence of surrounding involvement. *In situ* the organs occupied their usual positions, bound in a considerable amount of perirenal fat. Upon palpation they could easily be distinguished by their peculiar outline. If anything, they felt somewhat firmer than usual. There was no enlargement. Upon excision, attempting to dissect out the bodies from their surrounding fat, the usual brownish or yellowish character of the glands was found to have entirely

disappeared. Its place was taken in part by a fibrosis of the capsule and in part by an irregular trabecular type of firm, whitish tissue enclosing areas of softening more like a coagulation necrosis than an actual suppuration or caseation. The color of these softened areas corresponded to the color of the surrounding fat. If one had not been sure of the palpation of these organs and their position after excision and incision, nothing could be recognized which would fix their character. In other words the process present had involved the entire glandular structure, both cortex and medulla. The remaining substance was a mass of fat enclosing the capsule and trabeculae of fibrous tissue enmeshing areas of necrosis. This was a most unusual finding, the picture quite definite in itself and after a minute search no evidence of other similar involvement, with the exception of the healed caseous nodules in both apices, which were like all other similar lesions, could be found.

The kidneys were small, dark blue in color, bound down in considerable fat, capsules slightly adherent, cut edges bulged distinctly, cortex granular, with paler mottled lines. The pyramids stood out as almost pallid white islands in the midst of the kidney substance. There was no involvement of the ureters or bladder.

Upon dissecting out the retroaortic vessels several masses of glandular tissue were encountered. Some of these were distinctly hemolymph node types while others presented the fleshy character of lymphoid hyperplasia.

The pancreas had the usual salmon-pink color and upon section a normal meaty character. There was no fatty replacement and no fibrosis.

**Microscopical Examination. Kidney.** The section presents the pyramidal positions with increased hyalinized periglandular connective tissue. The cortex presents dilation and stasis of red blood cells in all capillaries, especially the tubular ones. In the endothelial cells of these capillaries and in the epithelial cells of the tubular epithelium there is a deposition of refractive granules of pigment. The tubular cells are swollen and granular, with distinct nuclei. The glomerules have slightly fibrotic capsules, desquamation of epithelial cells and some reduction in the size of the tufts.

**Diagnosis:** Chronic degenerative nephritis with passive congestion and metabolic pigmentation.

**Liver.** The section presents a diffuse appearance. The lobular structure is lost by reason of diminution of perilobular tissue. This is especially true of biliary capillaries and bile ducts. Decided atrophy of these elements is present. The central lobular veins are not distended but the interlobular capillaries are the seat of a diffuse but moderate stasis. Their endothelial lining cells are filled with granular pigment. The liver cells are not sharply defined but run into one another, with some obscurity of nuclei, and positions corresponding to the central lobular veins show vacuolization of fatty metamorphosis.

*Diagnosis:* Chronic degenerative hepatitis with diffuse passive congestion, fatty metamorphosis, metabolic pigmentation and atrophy of biliary system.

*Spleen.* The section presents a diffuse appearance and does not show the prominence of follicles noted grossly. The trabeculae are not thickened, but in places are prominent. There is a marked deposition of pigment of the same character as elsewhere, but in greater bulk. The lymphoid cells are closely packed and here and there endothelial cells have proliferated. Congestion is diffuse and stasis of red blood cells marked.

*Diagnosis:* Chronic lymphoid splenitis with passive congestion and metabolic pigmentation.

*Thyroid.* The section presents a compact picture of one of glandular activity. The epithelial cells are single layered, but show some proliferation as new glands. There are areas of lymphocytes and the capillaries are uniformly the seat of stasis of red blood cells. There is no pigment except in the endothelial cells of large vessel walls.

*Diagnosis:* Chronic interstitial thyroiditis with congestion.

*Pancreas.* The sections of pancreas present well-stained pancreatic cells, taking the usual predominance of basic color. The islands of Langerhans stand out clearly. All vessels, both capillaries and large, are filled with red blood cells, the same congestion as noted in other specimens. There is a diffuse deposition of pigment throughout the section not alone confined to the epithelial cells but decidedly concentrated in the midst of the cells of the islands of Langerhans.

*Diagnosis:* Congestion and metabolic pigmentation.

*Thymus.* The usual fibro-fatty tissue is present here with numerous large bloodvessels, and scattered throughout this are areas of lymphoid structure surrounding remnants of Hassall's corpuscles. The latter are small, flattened whorls of epithelial cells apparently containing congested red blood cells. In the lymph structure about these the type of cell is a small lymphocyte similar to those of the lymph node extending irregularly into the fatty connective tissue. There is no pigment present in this section.

*Lymph Nodes.* Numerous sections of lymph nodes taken from the peribronchial position show a large amount of pigment deposition, some of which is anthracotic, but a large amount of which is the same metabolic character as noted in the other sections. Capillaries are congested. There is a slight proliferation of lymphoid cells with irregular areas of endothelial cells, as noted in the spleen.

Retroperitoneal lymph nodes show the characteristic lymphocytic hyperplasia, congestion of the capillaries is moderate and only a small amount of pigment is present.

Sections taken from the retroaortic positions show numerous areas of lymphatic structure with markedly congested vessels. The

lymphoid proliferation is not as marked as elsewhere nor is the endothelial hyperplasia apparent.

*Adrenals.* There is no normal adrenal structure microscopically. There is a diffuse cellular proliferation, which cells are of several types—endothelial, plasma, endotheloid and fibroblastic. The endothelioids have grouped themselves into regular tubercle formation which in places has gone on to areas of necrotic hyaline and caseation. Here and there may be seen large giant cells. This process is not as sharply defined microscopically by the capsule of the adrenal, which in places is hyalinized, as it was apparently in the gross specimen; however, it does not penetrate to any considerable extent into the surrounding fatty connective tissue. As noted grossly the necrotic hyaline is more abundant than caseation, with a tendency to large conglomerate tubercles rather than miliary types.

*Diagnosis:* Caseous tuberculosis.

*Guinea-pig Test.* Subcutaneous emulsion of adrenal into two pigs. Both pigs died March 29, 1921. Autopsy showed identical findings. A small nodule over the site of the injection, tubercles with swelling and congestion in the spleen, liver, lungs and peribronchial lymph nodes. A small bloody exudate with some nodules on peritoneum.

*Smear from Spleen:* Tubercle bacilli positive.

*Comment.* Cases of true Addison's disease, tuberculosis of the adrenals, while they are not rare, are uncommon enough to warrant their report. In a study of this case there are several interesting features open to discussion and lines along which further work should be undertaken.

In the first place the presence of an advanced and directly confined active tuberculosis in both adrenals and the finding of a completely arrested and healed tuberculosis in the apices of the lungs is a hard one to explain. There has evidently been no fresh activity arising from the lungs. The apical infection may have preceded the adrenal infection or may have been coincident with it, or even the so-called healed lesions may have given up virulent tubercle bacilli which have secondarily lodged in the adrenals.

That this disease, at one time, must have been a bacteriemia, at least of a temporary nature, is quite evident. It would seem to the writer that the pulmonary lesions occurred at one time and were completely arrested while the adrenal lesion received its dosage through another portal of entry not apparent at the time of autopsy. The question as to whether a strain of tubercle bacilli with a predilection for the adrenal is only a supposition, and on the other hand any chemical combination which the adrenals might have had in attracting the tubercle bacilli to that particular site would, it seems to me, be a decided possibility. The complete absence of tuberculosis elsewhere in the body, in the presence of such an active lesion as found in the adrenals, offers a further field for study. That the

organisms had any predilection for the adrenal gland is more certainly ruled out by the fact that when inoculated into the guinea-pig they produced in duplicate the usual experimental tuberculosis.

The nature of the pigment, at least from its morphological character, would seem to be similar to that found in the hemozoin pigment of malaria, and indeed the distribution was very similar, being found in large quantities in the spleen and in the endothelial cells of capillaries throughout the sections.

That any of the other glands of internal secretion, as, for instance the thyroid or the retroaortic lymph nodes, were stimulated does not seem likely, although in the thyroid a distinct interstitial thyroiditis of a lymphoid nature was present.

The appearance of the capillaries in all of the sections showing a uniform stasis of red blood cells should be noted in the nature of a passive congestion with the characteristics of an active type. That the disease was due to a tubercle bacillus the case conclusively proves by animal experiment, in which the usual tuberculosis was produced and from which tubercle bacilli were cultured.

It is unfortunate that chemical studies were not carried out, either during the lifetime of the patient or upon the remnant of the adrenal gland obtained at autopsy. It would seem that the entire adrenal gland was eventually destroyed and replaced by a tuberculous process of a rather highly cellular character. That this produced a general diminution of adrenalin is quite apparent from the clinical history, but chemico-physiological studies of the gland remnant would have been interesting.

**Conclusions.** This report covers a case of Addison's disease presenting the characteristic clinical symptoms of progressive weakness associated with bronzing of the skin.

Pathologically the case presented a typical localized and focalized tuberculosis of both adrenals with an arrested apical pulmonary tuberculosis of a probable unassociated nature. The direct smear from the adrenal showed the presence of tubercle bacilli in large numbers. Animal inoculation with crushed material from the adrenal produced experimental tuberculosis from which tubercle bacilli were obtained in culture.



## REVIEWS.

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**X-RAYS AND RADIUM IN THE TREATMENT OF DISEASES OF THE SKIN.** By GEORGE MILLER MACKEE, M.D., Assistant Professor of Dermatology and Syphilology, College of Physicians and Surgeons, Columbia University; Fellow of the New York Academy of Medicine; Member of the New York Dermatological Society, New York Roentgen Society and Manhattan Dermatological Society; Member of American Dermatological Association, American Roentgen Society and American Medical Association; Former Editor of Journal of Cutaneous Diseases; Consulting Dermatologist and Syphilologist, St. Vincent's Hospital, etc. Illustrated with 250 engravings and 22 charts. Philadelphia and New York: Lea & Febiger, 1921.

THE first nineteen chapters, constituting about one-half of this book, are devoted to a general consideration of the physics of  $x$ -rays and radium, their biological effects and therapeutic action, and the method of application in the treatment of diseases of the skin. The author, unlike many others, has happily avoided the mistake of leading the reader into a bewildering maze of electrophysics that is entirely beyond the comprehension of the average physician (roentgenologists included) and leaving him stranded there, regretting all the while that he had not completed a course in electrical engineering before taking up the work of a radiologist. Instead his discussion of this phase of the work is relatively brief, but of sufficient length and detail to give a clear idea of the essential principles underlying the production of  $x$ -rays. The physics of radium and its emanations is treated in the same concise and clear manner. Valuable chapters in this section deal with the selection of  $x$ -ray apparatus, the amount and form of radium applicators, the arrangement of apparatus in the laboratory, the computation and charting of dosage, superficial and deep therapy, radiodermatitis and protection of patient and operator. The beginner will do well to study thoroughly and become familiar with the chapters dealing with burns and protection before attempting to use either the  $x$ -rays or radium as a therapeutic agent.

The latter half of the work is devoted to a discussion of  $x$ -rays and radium in the treatment of dermatological lesions, with explicit instructions as to the manner of their application. The author

very evidently realizes that these agents are productive of great harm when improperly handled and he therefore overlooks nothing in detailing his technic. He does not claim that his is the best technic that has thus far been evolved, but when one stops to consider that his knowledge is born of a vast experience accumulated by years of close study in a large clinic, we may safely accept it as standard. It surely gives us a comprehensive working knowledge such as we never before have had. The fact that conditions will doubtless arise that will warrant a modification of some of the author's methods, does not in the least detract from their value. The last, but by no means the least important, chapter deals with the medico-legal relations of roentgen and radium therapy. This chapter can be read with profit by any member of the medical profession, be he general practitioner or specialist.

The book contains one or two typographical errors, but is well written withal. The author, who is an acknowledged authority, has entirely accomplished his purpose in giving this work to the profession. He set out to produce a book in which the specialized training of the roentgenologist and dermatologist would be correlated and he has made a thorough job of it. All roentgenologists and dermatologists should be very grateful to him for having done so.

J. D. Z.

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TRAUMATIC SURGERY. By JOHN J. MOORHEAD, M.D., Professor of Surgery and Director, Department of Traumatic Surgery, New York Post-Graduate Medical School and Hospital. Second edition. Pp. 864; 619 illustrations. Philadelphia: W. B. Saunders Company, 1921.

THE second edition of this very useful work will be welcomed by the profession. The percentage of traumatic surgery seen by the general practitioner and the general surgeon is so constantly increasing that the importance of a wider knowledge of this subject is everywhere realized. Dr. Moorhead has revised the first edition of his work, so that this second edition includes many of the improvements gained by war experience. The subject of wounds, including bullet wounds, is dealt with in a concise and interesting chapter. The treatment of wounds according to their degree is systematically arranged, so that a novice in surgery can understand and follow it. In a similar manner the author deals with the subject of infected wounds. The Dakin-Carrel technic is given at length, together with the method for the preparation of Dakin's solution. Although the author discusses tetanus fully, he does not devote as much space to gas gangrene as the reviewer thinks necessary, especially with the ever-increasing number of cases seen in civil practice following traumatic wounds. The chapter on shock does not give adequate

attention to the value of blood transfusion in cases of shock associated with hemorrhage; however, in other respects it is admirable. The chapter on injuries of the joints includes a series of excellent roentgenograms taken from the *Murphy Clinics*, showing the blood supply in and around many of the important joints. Dislocations and fractures are dealt with in text-book style, and here again the author has included the appliances which were found of value in the treatment of military injuries. The use of the Thomas splint for fractures of the humerus and femur, together with the Blake-Keller femur splint and the Balkan frame, is carefully discussed and admirably illustrated. The only improvement one could desire for this chapter would be more attention to the caliper method of extension for fractures of the femur and both bones of the leg, since this has supplanted the "Codivilla-Steinmann nail extension method." The chapter discussing osteomyelitis falls short in its description of the treatment of chronic osteomyelitis, the author having completely omitted the excellent work of Chutro in this connection. Injuries of the head and spine have received the attention they deserve. Both subjects are thoroughly treated and the text is well illustrated. The same can be said of injuries of the chest and abdomen. It is to be regretted that the author found it necessary to include methods for nerve-lengthening and nerve-anastomosis, which, as has been said, if they do give results, are more attributable to luck than to good surgical technic. Injuries due to electricity, burns, heat-stroke, compressed air, illuminating gas, submersion and suffocation receive their proper attention. It is surprising, and yet enlightening, to see the relation of injuries to abortions, appendicitis, visceral prolapse and hernia discussed in so interesting a manner. The chapter on the traumatic neuroses should be read by everyone who has access to the book. It could not be improved upon. Standardized first-aid methods in accidents as related to industrial surgery are added in a new and final chapter.

I. S. R.

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PROSTHETIC DENTISTRY. By DOUGLAS GABELL, L.R., C.P., M.R.C.S., L.D.L., Dental Surgeon to the Royal Dental and Charing Cross Hospitals, Lecturer on Dental Mechanics to the University of London at the Royal Dental Hospitals. London: Oxford Medical Publication. Henry Frowde, Hodder & Stoughton, 1921.

A TEXT-BOOK of 234 pages, devoted to the chair side work for producing plate dentures. It is a book of unusual value to the student and recent graduates, as the subjects are fully and clearly treated, and would be the means of forestalling many unfortunate and avoidable failures. The concluding chapter on Complaints is a most unique, practical and useful one.

P. L. L.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Acute Circumscribed Edema (Quincke).**—H. QUINCKE (*Berl. Med. Klinik*, 1921, xvii, 675) analyzes 36 cases of "acute circumscribed" (angioneurotic) edema. The cases were evenly distributed among the sexes; the majority occurred between the ages of twenty-one and thirty years, the extremes being thirteen and sixty-eight years. The duration varied from a few weeks to thirty years; average five years. The duration of a single attack varied from a few hours to six days, commonly one and a half days. A single eruption lasted from ten minutes to twelve hours, the majority lasting five to six hours. The intervals between attacks varied from twenty-four hours to weeks, months or years (twenty-six years). In some cases there was some periodicity, the occurrences being daily at the same hour, or at longer intervals. A few cases showed a time relation to menstruation, either before, during, or after the period. Predisposing factors included psychic disturbances, overwork, postoperative hemorrhage, constipation, different types of food and drugs, sea-baths, warm baths, mechanical pressure, the rays of the sun, and toxins from foci of infection. Fever was present in a few cases. Thirty-nine per cent showed general nervous disturbances, and 13 per cent gave a suggestive hereditary history. A sedentary occupation seemed to be a predisposing factor in many cases. The swellings vary from 2 to 10 cm. in diameter, are raised, but not sharply marked off, either, pale, normal color, or reddened, and usually do not pit on pressure. There is a feeling of tension or burning, sometimes itching. Atypical forms and gradations of

Quincke's disease to erythema multiforme, erythromelalgia and Raynaud's disease were encountered. The most common site of occurrence of the swellings was the face (80 per cent), the eyes, lips, hands, arms, tongue coming next in frequency.

**Herpes Zoster Associated with Disease of Internal Organs.**—ARNSTEIN (*Wien. klin. Wchnschr.*, 1921, xxxiv, 13) describes a series of cases illustrating the occurrence of herpes zoster as the sole presenting symptom in diseases of internal organs. In an inflammatory disease of the liver, the herpes appeared along the course of the ninth thoracic nerve on the right. In a pulmonary infection in the left base, herpes appeared along the course of the fourth and fifth left thoracic nerves, later becoming generalized. In another case in which the left lower lobe was infiltrated, the lesions followed the course of the sixth thoracic nerve on the left. The course of the fifth thoracic on the right was affected in a case of involvement of the right apex, while an infection of the left apex was accompanied by a herpes at the level of the sixth left cervical nerve, and at the level of the third or fourth nerves in other cases. These areas correspond somewhat to the zones of Head, and the phenomena were explained on the basis that areas of lessened resistance resulted in the ganglia of the viscera-sensory reflex, followed by a hemorrhagic inflammation, from an infectious or toxic agent. The author suggests that all cases of herpes zoster should be examined for hidden internal lesions.

## SURGERY

UNDER THE CHARGE OF

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**Flocculation Reactions in Syphilis with Especial Reference to the Meinicke and Sachs-Georgi Reactions.**—LEVINSON (*Am. Jour. Syphilis*, 1921, v, 414) says that a brief *resume* of the numerous studies of the Wassermann reaction discloses two schools of thought (1) that which believes that the Wassermann reaction is an antigen-antibody reaction, and has attempted to modify and simplify this reaction; (2) that school which follows the study of the chemistry of the colloids and has attempted to show a parallelism between the Wassermann reaction and certain colloidal reactions. The latter has led to the Meinicke and Sachs-Georgi reactions. The Meinicke reaction is a test based on the hypothesis that the reaction between serum and extract takes place when extract colloids disturb the isotonicity of salt solution permitting the union of seroglobulins and lipoid extracts. This reaction is greatly intensified in positive syphilitic

serums as compared with negative. The various forms of Meinicke's reactions are the water method, salt solution method, and the third method, using an antigen prepared according to the method of Wassermann with the addition of horse heart extract. The Sachs-Georgi reaction is a physicochemical reaction between seroglobulins and lipid extracts. Phases 1 and 11 of the Meinicke reaction showed 89.2 per cent agreement with the Wassermann reaction; this reaction is in all respects characteristic for syphilis and it is more simple than the so-called third modification or Sachs-Georgi reaction. The third modification of the Meinicke reaction is more simple and is therefore recommended. The agreement with the Wassermann reaction is 88.8 per cent. In many cases it is positive earlier and often remains longer than the Wassermann reaction. The Sachs-Georgi reaction has met with the approval of many investigators. The non-specific reactions are less frequent with this test. None of these reactions can at present supplant the Wassermann reaction, but may be used in conjunction with it.

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**Viability of Spirocheta Pallida in Excised Tissue and Autopsy Material.**—LACY and HAYTHORN (*Am. Jour. Syphilis*, 1921, v, 401) say that from their experiments it is evident that spirochetes kept in serum or moist tissue, either human or animal, may retain slight motility as long as three months or more. Reliable dark-field examinations can be made on tissues or fluids collected several hours previously, provided they are kept moist and cool. The authors' results, which are in accord with those of Neisser, would indicate that complete drying is probably fatal to the *Spirocheta pallida*, since each of the rabbits inoculated with dried spirochetes on scalpels failed to develop syphilitic lesions. *Spirocheta pallida* may and in the author's case did remain virulent in autopsy material for twenty-six hours or longer.

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**Complement-Fixation Tests with Two Antigens.**—LARKIN (*Am. Jour. Syphilis*, 1921, v, 476) says that two antigens whose reliability has been established form a valuable check upon another for routine public health laboratory work. Cholesterinized antigen gave a high percentage of positive and doubtful reactions. This bears out the usual observation that cholesterinized antigens are more sensitive than crude alcoholic antigens. Sera are occasionally found which are undoubtedly positive but which, due to some peculiarity of the serum do not react with one of the antigens used. The cholesterinized antigen, used alone, must be considered a rather unreliable antigen likely to give false positives.

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**Studies in the Standardization of the Wassermann Reaction.**—KOLMER (*Am. Jour. Syphilis*, 1921, v, 439) says that the antibody content of serum from mixed venous and arterial blood collected by pricking a finger and of venous blood collected by venipuncture, is identical. Blood sera collected from fingers or by cupping are more likely to become anti-complementary than sera collected by aseptic technic and venipuncture, due to greater chances for bacterial contamination. Syphilitic sera collected at once by defibrinating and centrifuging blood contain as much complement-fixing antibody as

sera allowed to separate from one to forty-eight hours. When preserved human sera yield stronger complement-fixation reaction than the same sera while fresh, the difference is due to the presence of anti-complementary substances antilynsins or the deteriorations of natural hemolysins. The anti-complementary activity of a serum is greatly modified by whether it is used unheated or heated and by the presence or absence of natural hemolysins. The presence of anti-complementary substances (antilynsins) influences the degree of positiveness of a reaction and explains in part the differences observed with portions of the same blood in different laboratories; technic should, however, discover the presence of these antilynsins and render all laboratory reports uniform, insofar as positive or negative reactions are concerned. The serum control tube should not carry more serum or spinal fluid than the main tube or tubes if an anti-sheep or anti-ox hemolytic system is being employed in order to avoid the influence of natural hemolysis.

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**Salt Solution in Increased Intracranial Tension.**—FOLEY (*Surg. Gyn. Obstet.*, 1921, xxxiii, 127) says that intravenous injection of hypertonic salt solution or the ingestion of salt produces a fall of cerebrospinal fluid pressure and a diminution of brain bulk. In conditions of pathologically increased tension, the response is conditioned by the details of the pathological alterations. The determining factors appear to be the size of the lesion which increases brain bulk and the amount of fluid available for absorption. The induced fall of pressure is inversely proportional to the former and directly proportional to the latter. A distinction is made between increased intracranial fluid tension *per se* and increased intracranial tension which is due to enlargement of brain bulk. From observation of cases of obstructed and dilated ventricles an intraventricular absorption of fluid following salt ingestion seems to occur. The procedure has a definite field of clinical usefulness in cases exhibiting high grades of intracranial pressure. The most striking results are to be obtained in those cases in which cerebrospinal fluid obstruction exists.

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**Jejunal Ulcer.**—JUNN (*Surg. Gyn. Obstet.*, 1921, xxxiii, 120) says that gastro-enterostomy for ulcer of stomach or duodenum offers the patient a good prospect of complete and permanent relief of all symptoms. Unsatisfactory results are most often due to a gastro-jejunosomy in cases in which no ulcer exists—procedure must be upon a pathological basis. The relative appearance of the syndrome called “vicious circle” is due to recognition of the importance of avoiding operation when no ulcer exists. Jejunal ulcer is one of the most serious and perhaps one of the most common after-complications of gastro-enterostomy. It occurs either in the line of anastomosis as a so-called gastrojejunal ulcer or in the jejunum as a true jejunal ulcer. The lesion is usually single. Its frequency is difficult to estimate, Patterson reporting that they occurred in from 1 per cent to 2 per cent of cases. A satisfactory explanation of the cause of jejunal ulcer can best be found in the etiology of the original ulcer. Only one case of primary jejunal ulcer is mentioned in the literature. The author notes that jejunal ulcer following operation almost always occurs only following gastro-

enterostomy for ulcer. There have been no cases observed in the Mayo Clinic following plastic procedure around the pylorus. The principal cause of the secondary ulceration is the action of the acid gastric secretion on the mucous membrane of the jejunum. In all Patterson's cases and in more than 60 per cent of the cases in the clinic the acids were high even after gastro-enterostomy. Permanent suture material has also been a factor in the production of many ulcers particularly those close to the gastro-jejunostomy opening. Infection must play some part in the etiology of these lesions, for the cut surfaces of the stomach and of the jejunum are exposed to the infection from the original ulcer during operation and during the healing process, which lasts about fourteen days. The onset of symptoms varies from almost immediately after the gastro-enterostomy to eight or ten years. Usually all symptoms are completely relieved following gastro-enterostomy for six months to a year. The results of operations in these cases of secondary ulcer have been reasonably satisfactory, especially since the importance of dispensing with the gastro-enterostomy has been realized. Whenever a secondary ulcer has formed after gastro-enterostomy it is surprising how many will continue to form if the anastomosis is maintained in those patients who seem to have some definite irregularity or specific infection.

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**Studies in Reduction of Bone Density.**—PHEMISTER (*Am. Jour. Roentgenology*, 1921, viii, 355) says that reduction in density may be local, regional or general—according to the cause. The author's object is to show the histologic processes by which bone is destroyed. In bone infections there are four processes by which reduction in density may be produced—first, there is destruction of dead bone at the seat of greatest inflammatory activity; second, there is local destruction of living bone or caries; third, there is rarefying osteitis in the neighboring living bone for variable distances about the area of complete bone destruction; and fourth, there is regional atrophy of disease. In osteomyelitis necrotic bone results from the effect of the toxins in the most severely inflamed region. The unossified elements of the dead bone are rapidly killed by toxins and removed by the action of the serum and leukocytes. The calcareous deposits are only removed as a reparative process by the absorptive action of the granulations. From six to fifteen days elapse before signs of reduction in density can be shown by the  $x$ -ray. Tuberculosis usually produces localized osteitis. The metaphyseal region of the end of the bone is more frequently involved primarily, especially during the first decade. After the tenth year primary foci in the epiphyses are seen with increasing frequency. Ingrowth of tubercular granulation tissue beneath the articular cartilage is a common occurrence leading to destruction of the articular cortex of bone and to disappearance of the sharp line which it normally casts in  $x$ -rays. Bone syphilis produced gummatous caries in irregularly distributed and various-sized areas. Shadows from new bone formation are frequently interspersed. In bone tumors reduction of density results almost entirely from breaking down of living bone by cellular activity. In metastatic carcinoma of bones the relative amounts of bone destruction and new bone formation bear some relation to the seat of the primary tumor—and its degree of malignancy.



and rate of growth. Metastatic carcinoma of the breast tends to produce bone destruction with little associated new bone formation, while carcinoma of the prostate produces little bone destruction and much new bone formation. Reduction in density in sarcoma usually occurs *en masse* and while the outline of the area destruction may be irregular, extensive pocket formation is uncommon. New bone formation in the ossifying types of sarcoma may be sufficiently extensive to offset the reduction in density resulting from bone destruction but its distribution and arrangement are usually such that the shadows cast are of diagnostic significance. Central giant-celled tumors affecting the ends of the living bones form a special group and it is questioned whether they should be classified with sarcomas. They reduce bone density by eccentric growth and are entirely devoid of any tendency to undergo ossification. The reduction of density in bone cysts is quite similar to that in giant-celled tumors in that the process begins in the interior of the bone and produces eccentric erosion without subsequent ossification of the tissue which caused the erosion. Small perforations of the cortex are more common. The site affected is farther from the bone end.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**A Contribution to the Topographic Anatomy of the Thymus Gland with Particular Reference to its Changes at Birth and in the Period of the Newborn.**—NOVACK (*Am. Jour. Dis. Children*, August, 1921) studied 65 fetuses and full-term children. He found that the lobation of the thymus is determined early in fetal life, and the establishment of respiration has no effect on it. The thymus in the late fetus and in the newborn is predominately of the cervicothoracic type, with the position intermediate between the cervical location in the embryo and the thoracic location of the older infant child and adolescent. In the late fetus and in stillborn children there is a typical form and quite constant relations. Its lateral surfaces are convex and bulge against the medial surfaces of the lungs. The lungs very rarely extend at all on its anterior surface and the thymus very rarely extends at all on the anterior surface of the right ventricle of the heart. In liveborn infants it has a typical form and relation which are similar to those found in young children. It is elongated and molded so that the anteroposterior and lateral surface bear the impressions of all the organs with which it is in contact. The lateral surfaces usually show marked convexities, which are occupied by the lungs, which pass over the anterior surface of the organ. Unlike the fetal thymus it usually extends more inferiorly, passing over the right ventricle. The change from the broad or fetal type to the elongated and molded type found in the liveborn and in

young infants bears a direct relation to the establishment of respiration and is dependent on the expansion of the lungs. The organ is compressed from side to side by the medial surfaces of the expanding lung. It is compressed anteroposteriorly by the anterior borders of the lungs, which become much thickened in the establishment of respiration as they gradually overlap the thymus. In some cases the thymic substance may project posteriorly at birth to such an extent that some of the structures situated there are compressed by it. This may be due either to an unusually large thymus or to a very narrow superior thoracic aperture which will not allow the thymus to protrude into the cervical region as it is compressed by the expanding lungs. A distinction should be made between the broad fetal type and the infantile or narrow elongated type.

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**Calcium and Phosphorus in the Serum in Relation to Rickets.**—HOWLAND and KRAMER (*Am. Jour. Dis. Children*, August, 1921) found that in non-rachitic children the concentration of calcium is from 10 to 11 mg. per 100 cc of serum. The concentration of inorganic phosphorus is about 5 mg. per 100 cc of serum. The constancy of the concentration of calcium, phosphorus and bicarbonate in the serum of normal children undoubtedly determines the constancy of the inorganic composition of normal bone. During the period of active rickets the calcium concentration may be normal or slightly reduced. The reduction does not seem to depend directly on rickets. There are reasons for believing that in many instances the reduction is related to a latent form of tetany. The inorganic phosphorus of the serum is regularly reduced in active rickets, sometimes to an extreme degree. During the process of healing, whether occurring spontaneously or as the result of the administration of cod-liver oil, the phosphorus content of the serum gradually rises to a normal figure and often somewhat above this. Relapses are accompanied by a fall in the phosphorus concentration of the serum. All the children under two and a half years of age in whom there was an inorganic phosphorus content of the serum of 3 mg. or less had been suffering from rickets.

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**The Casein of Cows' Milk and Human Milk in their Relation to Infant Feeding (the Action of Rennin on Casein).**—BOSWORTH (*Am. Jour. Dis. Children*, August, 1921) found that the casein from cows' milk and human milk are acids, having the same chemical composition and the same chemical characteristics, the two caseins forming the same series of salts with bases. In cows' milk the casein is present as a calcium caseinate, while in human milk the casein probably is present as a potassium caseinate. When rennin is added to solutions of casein or to milk the casein is split into two equal molecules of paracasein. The addition of rennin to solutions of casein or to milk may or may not result in coagulation, depending on the nature of the salts in the solution or milk. Coagulation is promoted by soluble calcium salts and is retarded or inhibited by the addition of soluble salts of sodium, potassium or ammonium. The development of acidity in cows' milk favors coagulation after the addition of rennin; the greater the acidity the tougher the curds. Milk in entering the infant's stomach is acted upon by the enzymes present. The enzyme rennin, acting upon casein,

changes it to paracasein. Breast milk contains small amounts of casein and small amounts of soluble calcium with relatively large amounts of sodium and potassium. The action of rennin on breast milk results in no curdling or the production of a very small amount of very finely divided curds. Breast milk enters the mouth, stomach and intestines in a liquid state. It does not form large curds in the stomach and cannot block the pylorus. Cows' milk or any of its modifications contain large amounts of casein and soluble calcium with relatively small amounts of sodium and potassium. The action of rennin on these milks or their modifications, owing to the high casein and soluble calcium contents, results in the production of large flocculent curds, which at body temperature may coalesce and form large masses. These masses are a mixture of paracasein, fat and milk salts. Cows' milk or any of its modifications enters the mouth and stomach as a liquid, but in the stomach a part of the milk may be separated into curds by the action of the rennin. These curds may become very large and may block the pylorus. They may remain in the stomach for days and may be added to by subsequent feedings. Fresh cows' milk does not curdle on addition of rennin. Curd formation depends on acidity.

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**Lesions of the Corpus Striatum in Childhood, with a Report of Clinical Cases (Illustrating Various Syndromes).**—CROTHERS (*Am. Jour. Dis. Children*, August, 1921) says that a number of syndromes characterized by disturbances of associated movements, variation in muscle tone and speech defects are definitely associated with sharply defined localized lesions of the corpus striatum. They are easily distinguished in typical cases from spastic pyramidal tract syndromes and from ordinary chorea. In atypical cases confusion arises and careful sorting out of signs is necessary. Critical reëxamination of children showing involuntary movements over a period of months or years reveals unsuspected cases. The cases of this series demonstrate the dangers of relying on casual impressions in judging mental states when speech defects and motor disorders complicate the picture. From every point of view the study of cases of the type described here is well worth while. The present classification is purely tentative and is too rigid. The author's experience indicates that these disorders are not rarities, but that general attention to them has not been stimulated. The corpus striatum may not be the only area involved. Many other lesions may complicate and obscure the picture.

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**Some Observations on the So-called Inanition Fever of the New-born.**—GRULEE and BONAR (*Arch. Ped.*, July, 1921) reported at the meeting of the American Pediatric Society that they had studied 183 newborn infants with regard to the transitory fever which frequently occurs during the first few days of life, and which has not been accounted for satisfactorily. It is apparently a febrile condition simple in nature. Observations were made on the weight for the first five days; the percentage of greatest loss; the highest daily temperature for five days; the quantity of breast milk for this time period; the quantity of water for the same length of time; the total foods taken for these days; the estimated loss by vomiting; the total number of stools; icterus if present and upon what day it appeared. The cases were divided into groups

according to weight. For normal cases the average weight loss was 6.2 per cent; for 46 cases with a temperature between  $99.2^{\circ}$  and  $100^{\circ}$  the weight loss was 6.2 per cent; for 16 cases with a temperature between  $100.2^{\circ}$  and  $102^{\circ}$ , the average weight loss was 11.2 per cent. While at first glance this appeared to be significant, if the individual cases were carefully examined it would be found that among the cases with normal temperature the loss of weight was as great as 17.3 per cent, which was higher than any case with fever. There could not be shown any regular relationship between the quantity of fluids ingested and the occurrence of fever. Some cases seemed to show a relationship between the fever and the food ingested, but others seemed to give an opposite result. The conclusion was made that the temperature rise was not regularly to be explained on the basis of dehydration. It has been suggested that the temperature elevation may be due to the absorption of some protein product, either bacterial or other.

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**Malnutrition in Children of the Well-to-do.**—KERLEY, LORENZE and DuBOSE (*Arch. Ped.*, July, 1921) presented this paper at the meeting of the American Pediatric Society. They described a type of cases of malnutrition where the child remained persistently an inferior individual from a physical standpoint. In the majority of these cases two features stood out prominently. These were deficient food intake or imperfect digestion, though the caloric intake was not necessarily below the normal requirements. It was found that these cases fell into groups. First there were those cases in which there was a maladjustment of the different food elements. Usually butter cream and 4 per cent milk fat had been crowded. From the caproic standpoint the children had been fed above their requirements on a non-growing diet. The essential foods, meats, cereals, vegetables and fruits were taken indifferently. In the management of these children the fact must be recognized that there must be a healthy desire for food, and this can be created by the withdrawal of fats and sugars in large measure. Three meals should be given daily at five-hour intervals, and nothing but water should be allowed between meals. A low fat and sugar diet should be given. In the second group hyperacidity of the stomach juices causes a defective food intake and malnutrition largely through the production of a poor appetite. The chief symptom of hyperacidity is a lack of desire for food. In cases of long standing this is accompanied by nausea and vomiting. Pain and discomfort are greatest before the meals. Gastric analyses were made in 51 cases between the ages of two and eight years. A total acidity ranging from 38 to 138 was found. Normal acidity is usually considered as ranging from 30 to 40. In this group etiological factors include candy and ice-cream, irregularity in meal hours and faulty feeding. This type of patient usually responds to dietetic treatment. Three meals suitable for the age are to be given and nothing is allowed between meals except water. Extremes of heat and cold should be avoided. Condiments, candy, pastry and raw fruits are excluded. It is important that a daily evacuation of the bowels be ensured. The third group of cases comprise those in which defective intestinal mechanics delay the emptying of the stomach. Defective food intake and poor appetite are usually found in those in whom there is a stomach residue after four and a half hours. In order that a child have a normal

desire for food there must be an interdigestive period of at least one hour. Retention is sometimes due to pylorospasm caused by an anomaly or lesion lower down in the intestinal tract. Some of these include ptosis, angulation, dilatation and sacculation. The fourth group, although comparatively small, include the hardest type to effect relief. These were the underweight, overactive, anemic, physically retarded, precocious children.

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**Acute Rheumatic Fever and Its Variants in Childhood and Adolescence.**—RIESMAN (*Jour. Am. Med. Assn.*, May 21, 1921) points out that in childhood this disease presents certain important peculiarities. Although it occurs in children of all ages, even having occurred intra-uterine, it is most frequent between the ages of five and fifteen years, and is especially common about the age of puberty. Girls seem to be affected a little more frequently than boys, while in the adults the males are more frequently affected. The joint involvement is often slight and may be overlooked. He reminds us that growing pains, so called, are frequently rheumatic signals. The involvement of the heart is very common in children. Its occurrence and severity bear no relationship to the severity of the joint involvement, as slight joint involvement may be followed by severe damage to the heart. Follicular tonsillitis frequently precedes the attack and is commonly found in the previous history of the patient. Chorea often follows attacks. In children there is more frequently skin manifestations than in adults. Cerebral rheumatism characterized by delirium and hyperpyrexia is rarely seen in children, but it is a complication of the disease in the adult.

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## OBSTETRICS

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UNDER THE CHARGE OF

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**Treatment of Sterility by the Use of the Intra-uterine Stem Pessary.**—RAWLS (*Am. Jour. Obst.*, February, 1921, p. 499) publishes the result obtained by the study of 205 cases with final results in 117 cases. In 47 cases, or 22.9 per cent, sterility was the condition for which relief was sought; in 23, or 11.2 per cent, dysmenorrhea and sterility were the reason for the treatment. In some of the cases before the pessary was introduced dilatation and curetting were done. When the scraping were examined microscopically they were normal in 68.8 per cent. The hard-rubber stem pessary was used in 54.8 per cent of the cases, the glass stem in 43 per cent, the straight in 40, the curved in 40 and the Wylie drain in 4 or 2.2 per cent. In 124 cases the pessary was worn in 16 less than a month; in 36 from one to two months; in 24 from two to three months; in 15 from three to four months; in 3 four to five; in 1 five months and in 29, or 23.4 per cent, the pessaries were cut out

partially or entirely. When hard-rubber pessaries were used sutures of silkworm gut were employed to keep them in place; when glass pessaries were selected suspension sutures were secured by shot or washers or bone buttons. While many of the symptoms and conditions present are of interest the obstetrician has to do only with the question of the use of this pessary as an aid in remedying sterility. It was found that the method of treatment has a limited field of usefulness and in about half of the patients presenting themselves with pelvic conditions this pessary could be used. As an operative measure it is applicable to 2.3 per cent of patients treated and 1.3 per cent of operations performed in hospital. The treatment is not without its complications and disadvantages, for while a temporary rise of temperature is not unusual there is a transient morbidity of 17.6 to 21.8 per cent and a permanent morbidity of from 5.8 to 9.8 per cent. For sterility it is stated that relief followed its use in 23.4 per cent. Comparing it with other forms of operative interference it is said to give as good results as other operations, with less primary invalidism and no more liability to permanent bad results. This treatment should never be used except in carefully selected and studied cases, when its results should be correspondingly good.

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**Indirect Expulsion of the Placenta.**—BAER (*Jour. Am. Med. Assn.*, February 26, 1921) expresses the placenta by taking the abdominal wall in the two hands, drawing it together and compressing the uterus in longitudinal direction. This is done just above the uterus in such a way as to force the uterus down toward the pelvic brim; the patient is urged to bear down during this time. By this manipulation the recti muscles are pulled together and held firmly. Four hundred cases were so treated by nineteen operators. In the majority of cases this method was successful within thirty minutes after delivery of the child; in eleven cases forty-five minutes elapsed and in one case three trials were made and the placenta expressed in sixty minutes after the birth of the child. The method is stated to be 90 per cent efficient in the hands of different operators.

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## GYNECOLOGY

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**Drainage in Pelvic Surgery.**—The question of when to drain in the performance of pelvic operations is a never-ending question and from the extreme of universal drainage of some years ago, the pendulum has

almost swung to the point where drainage had to be defended by the surgeon using it. The question can only be answered by long and varied experience under all sorts of conditions and there is probably no gynecologist in this country whose opinion along this line should bear more weight than Kelly's (*New York Med. Jour.*, 1921, cxiv, 390). He feels sure that from time to time the judicious use of a drain over a short period of time, from thirty-six hours to several days, does one of three things: It is an unspeakable comfort to the surgeon to be sure that there is no collection of fluids about the field of operation. It relieves the patient of a vast amount of discomfort in her early convalescence, converting a stormy, febrile recovery into a smooth, peaceful one. It carries off the serum and blood, and, it may be, lingering infections which occasionally give rise to a general peritonitis. Kelly would drain in every case where infectious material has been widespread and there remain some lingering suspicious areas. He includes here cases in which there has been soiling by bowel contents. He would drain in all ragged cases such as those in which pelvic adhesions had been so extensive and firm about the floor and walls that the occurrence of considerable sero-sanguineous weeping is a moral certainty. Without exception, he drains after removing a cancerous uterus. He uses a small, special drain in most cases of myomectomy, where sometimes weeping and bleeding occur unaccountably. When in serious doubt, Kelly says "drain!" Some surgeons would undoubtedly reverse this dogma. If the trouble in the pelvis is very severe, then a good, big drain of washed iodoform gauze in protective rubber tissue ought to be laid through the vaginal vault, to cover the pelvic floor loosely. It should never be packed in tightly and never, under any circumstances, should the drain be allowed to extend up or down between loops of bowel. A form of drain which he has found most useful in his work, and which he calls a provisional or tell-tale drain is a small drain about the size of a cigarette or a little larger. It is peripheral in two senses, it is laid through the abdominal wall at or near the lower angle of the median incision, above the symphysis, reaching well within, but no attempt is made to come into contact with the field of the operation which lies, it may be, well below the pelvis. He uses such a drain in myomectomy as well as where serious oozing is to be expected, but never where there is reason to expect immediate infection. Its sole function is to let out all the excess of serum and blood welling up from the pelvis and seeking this direction of least resistance. It is temporary in character, being removed in from twenty-four to thirty-six hours, as soon as the outward flow abates, as shown by the dressings remaining dry.

**Embolism after Hysterectomy for Myoma.**—A patient has had a hysterectomy for a uterine myoma and has had a satisfactory recovery and is about to be allowed out of bed, the family having been assured that complete recovery is merely a matter of time, when suddenly, the patient collapses and death ensues in less time than it takes to describe. Such is the sad picture of pulmonary embolism as it occurs in a small percentage of cases following pelvic operations and we stand helplessly by when the condition occurs, realizing that our efforts are futile. Any investigation which would reduce the incidence of such a dreaded complication would undoubtedly receive recognition from the

profession and therefore we desire the reader to become acquainted with the work of Farrar (*Am. Jour. Obst. and Gynec.*, 1921, ii, 286) based on observations in the Woman's Hospital in New York. She finds that pulmonary embolism or thrombosis is the most frequent cause of postoperative pulmonary complications following hysterectomy for myoma uteri and the source of the embolism is a thrombosis of the pelvic veins or the veins of the lower extremities, or a thrombosis of the right heart. The development of a thrombosis or embolism may be during an operation or immediately following it. The most frequent time seems to be during the first forty-eight hours. The symptoms in the order of their most frequent occurrence are pain, friction rub, cough, bloody sputum and rales, dulness and alteration of breath sounds. These signs are premonitory of a thrombosis but the evidences of thrombosis in the veins of the lower extremity or pelvic veins do not appear until later. The physical findings at the onset are similar to lobar pneumonia or pleurisy, but the clinical picture soon separates the cases. In differential diagnosis the roentgen ray may be of value. The causes of thrombosis are: (1) An enfeebled circulation due to: (a) dilated venous trunks, especially of the pelvis and lower extremities; (b) venous stasis; (c) lowered blood volume due to hemorrhage or shock; (d) myocardial insufficiency. (2) Infection. The treatment of this condition should be prophylactic and directed to improving the circulation of the blood by strengthening the heart muscles and walls of the blood-vessels and increasing the hemoglobin of the blood. The importance of rest in bed as a preliminary to operation to relieve the pressure of large myomata on the veins of the pelvis and lower extremities, the use of blood transfusion *before* operation in cases of marked anemia and the maintenance of the blood volume during operation by gum glucose given intravenously, should be emphasized. In substantiating this theory, Farrar reports that during a two-year period all ward patients having large fibroids were kept in bed from five to seven days prior to operation and no embolism or thrombosis occurred in any case. In the private patients, who were not kept in bed prior to operation, a fatal embolism occurred once and venous thrombosis six times during the same period with exactly the same operative technic.

**Management of Renal Tuberculosis.**—Looked at broadly the development of our knowledge of renal tuberculosis within the last ten years has been satisfactory, according to CABOT (*Minnesota Med.*, 1921, iv, 354). The relative frequency of the disease, its accurate diagnosis and its satisfactory operative treatment have been developed progressively and soundly, and the improvement is nowhere better shown than in the operative mortality. Prior to 1900 the mortality for nephrectomy for tuberculosis was at least 25 per cent, while at the present time the mortality in the great clinics is between 2 and 3 per cent. Considering the technical difficulties of the operation of nephrectomy, the proximity of important structures, including the great blood-vessels and the rather poor condition of these patients, this is a highly satisfactory showing, and we might be satisfied if we did not turn our attention to the end-results. The study of the results in several large series of cases taken from various clinics where results are known after a lapse of years shows that we cannot yet rest from our labor. Roughly



speaking it shows that of 97 to 98 per cent of the cases who leave the hospital after nephrectomy for tuberculosis about 25 per cent die of urinary tuberculosis, and of this number one-half die within the first two years and the balance within five years. In such cases the author believes that they either had tuberculosis of the remaining kidney, though unsuspected, or they must have developed it very promptly after operation. There is no method now at our disposal which will enable us to diagnose "closed" tuberculosis, not the form in which closure of the ureter has resulted, but those tuberculous lesions of the kidney which are contained entirely within the renal parenchyma and communicate at no point with the renal pelvis. These cases undoubtedly exist and show a urine indistinguishable from the normal. As a result of his study of the problem the author believes that in a certain number of the cases we must expect tuberculosis of the remaining kidney as an unavoidable consequence of the operation, and he states there is nothing which we can do to avoid its occurrence, and it must therefore be charged off to depreciation. There is another possibility of infection occurring after operation, namely, infection of the remaining kidney as a consequence of the measures taken to arrive at an accurate diagnosis. Diagnosis of sufficient accuracy to warrant operation depends inevitably upon cystoscopy and ureteral catheterization. The majority of these patients have tuberculosis of the bladder secondary to their renal disease. In many of them the technical difficulty of the examination is great and trauma nearly or quite unavoidable, and were we dealing with any other form of infection of a unilateral type we should be gravely conscious of the danger of infecting the remaining sound kidney. This has been largely overlooked, and though it may be regarded as inevitable to accurate diagnosis, we must overhaul our methods and be sure that they expose the patients to the slightest possible danger of infection.

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## PATHOLOGY AND BACTERIOLOGY

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**Experimental Rickets in Rats. I. A Diet Producing Rickets in White Rats and its Prevention by the Addition of an Inorganic Salt.**—SHERMAN and PAPPENHEIMER (*Jour. Exper. Med.*, 1921, xxxiv, 189) indicate advantages of using rats for the experimental study of rickets, calling attention to the close resemblance of the lesions to those of human rickets, the ease with which controls of the same litters can be obtained, the rapid development of the lesions, the elimination of

variations in susceptibility, the possibility of working with large numbers, the economy of space and expense and finally the easy manner in which histological examination of bones can be carried out. With no failures fifteen rats were rendered rachitic by a diet consisting of patent flour (95 per cent), calcium lactate (3 per cent), sodium chloride (2 per cent) and in some ferric citrate (0.1 per cent). The substitution of 0.4 per cent secondary potassium phosphate in the diet completely inhibited the development of rickets. Quantitative determination of calcium in the bodies of parallel rats showed a marked increase of calcium content in the rats receiving the added phosphate over those which developed rickets. "While it was shown by the roentgen rays, by histological examination and by quantitative chemical analysis that added potassium phosphate increased the assimilation and normal depositions of calcium, it may be the quantitative relationship between the inorganic ions rather than actual deficiency of any one of them which was here the determining factor in the cause or prevention of rickets." The authors state that their experiments and conclusions do not exclude the possibility of other causes of rickets than those discussed by them.

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**Note on the Preservation of Stock Strains of *Treponema Pallidum* and on the Demonstration of Infection in Rabbits.**—BROWN and PEARCE (*Jour. Exper. Med.*, 1921, xxxiv, 185) have been able to dispense with serial transfers of stock strains of *Treponema pallidum* by keeping a sufficient number of infected animals to guard against loss of the strain by their death. When it is desired to recover the organism a popliteal lymph node may be excised, aseptically, minced, ground in a mortar and an emulsion prepared by the addition of 1.5 cc sterile normal salt solution. One half cc of this emulsion is then injected into a testicle of one or more rabbits. The inoculation should be made six to eight weeks before the organism is needed. The same method is applicable for the demonstration of infection in experimental animals. The authors caution that atrophy of the testis may occur instead of the usual granulomatous enlargement and, in exceptional instances, infection may be recognized by the development of an adenopathy when no lesions can be detected at the site of inoculation. The method is based on the experimental evidence that there was a constant invasion and localization of the organism in the superficial lymph nodes, that the infection persisted indefinitely and that the organism could be recovered at any time from such nodes as the popliteals.

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**Bacteriologic Studies of the Upper Respiratory Passages.**—In a series of four articles PILOT and PEARLMAN (*Jour. Infect. Dis.*, 1921, xxix, pp. 47, 51, 55 and 62) report bacteriological investigations to determine the incidence of hemolytic streptococci in the adenoids and of pneumococci, non-hemolytic streptococci, influenza bacilli (Pfeiffer), diphtheria bacilli and diphtheriods in the tonsils and adenoids. From cultures of 25 nasopharyngeal swabs and the surfaces of 78 extirpated adenoids from children hemolytic streptococci were recovered in 55 per cent, while from the crypt-like depressions of the adenoids of the same persons they were found more abundantly in 61 per cent. The excised tonsils of the same persons revealed hemolytic streptococci in

large numbers in 95 per cent. In a series of 103 adenoids pneumococcus occurred in 65 per cent,—2 per cent of which were type II, 13 per cent type III and 85 per cent type IV. In the nasopharyngeal swabs of 21 persons the pneumococcus was recovered in 71.4 per cent and from the tonsils of the same persons in 66 per cent and the adenoids in 71 per cent. They occurred more numerous in the crypts than in the swabs. *Streptococcus viridans* was found in 89 per cent of adenoids and 81 per cent of tonsils, while *Streptococcus mucosus* was encountered in 3 per cent of adenoids and indifferent streptococci in 12 per cent. Mather's coccus was noted in 17 per cent of adenoids. Gram-negative, pleomorphic and hemoglobinophilic bacilli, presumably *Bacillus influenzae*, were isolated in 40 per cent of extirpated adenoids and in 53.9 per cent of excised tonsils from 115 persons. In the nasopharynx they were present in 40 per cent of 25 persons. *B. diphtheriae* were found 12 times in the excised adenoids and extirpated faucial tonsils of 100 children, being encountered in both the adenoids and tonsils of the same individuals. Two of the 12 strains were virulent. Diphtheroids occurred in 30 per cent of the adenoids and in 17 per cent of the tonsils. In an additional investigation, MEYER, PILOT and PEARLMAN (*Jour. Infect. Dis.*, 1921, xxix, 59) found that removal of the tonsils and adenoids in children decidedly reduced the number of hemolytic streptococci and influenza bacilli, and to a less extent the pneumococci in the oropharynx and nasopharynx, but did not cause their disappearance.

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**Relation between the Virulence of Streptococci and Hemolysin.**—STEVENS, BRADY and WEST (*Jour. Exp. Med.*, 1921, xxxiii, 223) determined the relation between the hemolysin production and the pathogenicity of five strains of *Streptococcus pyogenes* (Holman). Avirulent organisms were obtained by frequent transplants on blood agar for several months. The same strains were rendered virulent by repeated passages through mice, after which the virulent and avirulent forms were transplanted to horse serum broth, and fourteen to eighteen-hour cultures were seeded into trial flasks of the same media. After centrifuging, the supernatant fluid was titrated against mouse cells to determine the hemolytic titer and this was done at frequent intervals until after the maximum hemolysin production had occurred. In this way, determinations were made with actively growing organisms which were accustomed to the media in which the tests were made. The results showed that both the virulent and avirulent forms of each strain produced, at some time during their growth, approximately the same maximum hemolytic titer. There was a tendency for the original culture to grow more rapidly than the more pathogenic forms and to reach the height of hemolysin production at an earlier stage during the growth of the culture.

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**Acute Respiratory Infection in Man Following Inoculation with Virulent Bacillus Influenzae.**—During the past few years a large number of persons have submitted themselves to inoculation experiments where filtered or unfiltered nasopharyngeal secretions from individuals with influenza, as well as pure or mixed cultures of the ordinary bacteria, have been instilled into the upper respiratory passages. Following the observations of Blake and Cecil on monkeys, CECIL and STEFFEN

(*Jour. Inf. Dis.*, 1921, xxviii, 201) inoculated healthy human volunteers with strains of *B. influenzae*, extracts of *B. influenzae*, *Streptococcus hemolyticus* and pneumococcus. Six persons received suspensions of *B. influenzae*, freshly isolated from chocolate blood agar cultures or from the peritoneal cavity of monkeys or from chocolate blood broth cultures. One volunteer was a carrier of influenzal bacilli, while three of the six had had influenza in 1918-19. All materials were administered into the anterior nares in a small quantity of fluid (0.5 to 1 c.c.). It was found that the virulent influenza bacilli excited in the volunteers "an acute respiratory disease similar in many respects to influenza, but falling short of the typical clinical picture." The authors suggested that their success could be attributed to the fact that freshly isolated, virulent strains were used and believed that fluid cultures and washings from animal exudate produced better results. Influenza bacilli, biologically identical with those inoculated could be recovered from the discharges as long as symptoms persisted and often for some time thereafter. Two individuals received filtrates of *B. influenzae* cultures, both of whom showed neither local nor constitutional reaction. One of the two volunteers who were given virulent hemolytic streptococci from human sources developed an acute tonsillitis. Negative results were obtained in the two persons who received a virulent pneumococcus type IV.

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**Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients.**—Much has appeared concerning the cause of epidemic influenza in the recent literature. Positive and negative results have been obtained by various investigators employing Pfeiffer's bacillus and other organisms as well as unfiltered and filtered nasopharyngeal washings in both man and animals. OLITSKY and GATES (*I, Jour. Exp. Med.*, 1921, xxxiii, 125) inoculated rabbits with unfiltered nasopharyngeal washings, filtered washings, lung tissue suspensions (filtered and unfiltered) from previously inoculated rabbits, similar lung tissue preserved in sterile 50 per cent glycerol, bacteria and culture materials and control materials. Three c.c. of these materials were introduced directly into the lungs under light ether anesthesia, through an intratracheal catheter, by a modified Lamar and Meltzer method or by tracheotomy. The studies were performed during the first epidemic wave in 1918 and 1919, the second of the autumn of 1919, and the third in the winter of 1920. The nasopharyngeal materials were obtained from those cases of acute uncomplicated influenza which presented a sudden onset with chilliness, fever, prostration, headache, muscular pains, injected conjunctivæ, sore throat and an unproductive cough. Great reliance was placed on leukopenia affecting the absolute number of the mononuclear cells, chiefly of the lymphocytic variety. The unfiltered nasopharyngeal secretions from eight cases of uncomplicated influenza in the first thirty-six hours of the disease, and from twelve cases in the later stages of the infection, were inoculated into the lungs of rabbits. The washings from seven of the eight early cases produced fever, indisposition, listlessness, ruffled hair, conjunctivitis and a marked leukopenia in the rabbits. The symptoms began in from twenty-four to forty-eight hours after inoculation and persisted for about three days, the animal then returning to normal. If the

rabbits were killed, edema, emphysema and hemorrhagic foci were found in the lungs. Similar syndromes were produced by successive passages of lung-tissue suspensions, the aerobic cultures of which were usually sterile. The material from the twelve cases that were either afebrile or convalescing or in the course of a secondary pneumonia produced no symptoms in the rabbits. All the control tests, which consisted of the injection into the lungs of rabbits of a saline solution, suspensions of normal rabbit lungs, normal rabbit serum, foreign protein, ordinary bacteria, including Pfeiffer's bacillus and its toxin as prepared by Parker's method and, finally, the nasopharyngeal secretions from fourteen apparently healthy persons, failed to show the "familiar clinical and pathological action." The same authors (*II, Jour. Exp. Med.*, 1921, xxxiii, 361) obtained negative results when nasopharyngeal secretions from early cases of uncomplicated influenza were inoculated, intratracheally and subconjunctivally into *Macacus rhesus* monkeys. On further experimentation, it was found that the "active agent," as it existed in the nasopharyngeal secretions in man and in the lung of rabbits injected with human secretions, passed through Berkefeld V and N candles and was capable of producing the same effects in rabbits as the unfiltered material; that the peculiar effect encountered in the inoculated rabbit could be induced in guinea-pigs and the "agent" withstood the action of sterile 50 per cent glycerol for periods up to nine months. The effect on the rabbit lung of pure cultures of types of organism ordinarily encountered in the aerobic cultures of human nasopharyngeal secretions, alone or in combination with the "influenzal agent," was studied (*III, Jour. Exp. Med.*, 1921, xxxiii, 373). It was found that neither *B. Pfeifferi* nor its toxic extract when injected intratracheally into the lungs of rabbits induced changes similar to those described for the "influenzal agent" or produced a pneumonic consolidation or led directly to the death of the animals. From their works in this series the authors concluded that concurrent infections in the experiments described could be regarded as of accidental nature and were not causally related to the typical effects induced in rabbits by a material wholly free from ordinary bacteria and that the "influenzal agent" exerted an effect on the pulmonary tissue which encouraged the invasion of the lung and subsequent multiplication there of ordinary bacteria. They believed that a similarity existed between the conditions under which concurrent infections arose in the inoculated rabbits and those which seemed to favor the occurrence of concurrent infection during epidemic influenza in man. They call attention to the fact that death did not occur in rabbits as a result of the uncomplicated effects of the "influenzal agent" alone, death being seen only in those animals where concurrent infection of the lung by ordinary bacteria was present.

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**Albumin Reaction in Sputum.**—Conclusions as to the value of albumin reaction as a diagnostic aid in tuberculosis have varied with different investigators since the first determination of Biermer in 1885. BURDICK and GAUSS (*Am. Rev. Tuberc.*, 1921, iv, 889) reported the results obtained in examining the sputum of 200 patients. Equal parts of sputum and 3 per cent acetic acid were mixed and the clear filtrate was tested by using the Esbach albuminometer tube commonly

employed in urinalysis. Albumin was found positive in 95 per cent of the patients with incipient, in 98.4 per cent of those with moderately advanced, and in 92.6 per cent of those with advanced tuberculosis. It was present in 26 unclassified cases of pulmonary tuberculosis and of all the tuberculous individuals examined, 96.3 per cent had a positive test. In 6 patients with chronic bronchitis and 2 with asthma, no albumin was found in the sputum, whereas 1 case of lobar pneumonia showed the presence of albumin. It was found that the quantity of albumin varied in the various cases from day to day. From their own investigations, the authors concluded that the test is of value as a diagnostic aid in pulmonary tuberculosis.

**The Incidence of Bovine Infection in Tuberculous Meningitis.**—Some investigators have found 15 per cent of tuberculous meningitis cases in man due to bovine strains. That 49 per cent of the cases in children under five years' of age and only about 1 per cent in adults are of the bovine type is startling. NOVICK (*Jour. Med. Res.*, 1920, xli, 239) studied 48 strains of tubercle bacilli from the cerebrospinal fluid of as many unselected cases. Three of these were of bovine type. Indirect isolation was accomplished by subcutaneous injection of the guinea-pig, pure cultures being obtained by culture of inguinal lymph nodes on Dorset's plain egg or glycerin egg media. It was found that, while a moist growth on Dorset's medium was usually indicative of the bovine type, confirmation by demonstration of virulence in the rabbit was necessary. To a degree, the production of pigmentation on egg medium suggested a human origin of the tubercle bacilli, but this characteristic depended upon the age of the culture.

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## HYGIENE AND PUBLIC HEALTH

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**Studies of the Phenomenon of d'Hérelle with *Bacillus Dysenteriae*.**—WOLLSTEIN (*Jour. Exp. Med.*, 1921, xxxiv, 467) states that the phenomenon of d'Hérelle is the expression of a lytic reaction occurring between a bacterium which is inducing an infection in an animal and a substance elaborated in that organism, probably by the leukocytes and other tissue cells, in response to the stimulus of the metabolic products of the invading bacterium. The important element

of the reaction is that bacteria exposed to the lytic substance acquire the ability to transfer the lytic property to subsequent generations. It has been shown that a lytic fluid for dysentery bacilli can be obtained from the peritoneum of the guinea-pig by intraperitoneal inoculation of live dysentery bacilli, and that the lytic action of such a fluid is not strictly specific, but that it exerts a group action on the dysentery-colon-typhoid group of bacilli. A lytic fluid with similar effects was obtained from a child dying of Flexner dysentery infection, and an anti-colon bacillus lytic fluid from a child who died of intussusception with colon bacillus peritonitis. The action of the lytic fluid on the dysentery bacilli, both in vivo and vitro, is to divide the culture into sensitive and resistant strains, and the latter can be carried to a degree of very marked, if not complete resistance to lysis. Such resistant strains are not lysogenic, nor are they agglutinable. The sensitive strains are lysogenic and agglutinable. Varying degrees of sensitive and resistant bacilli exist in a single culture. The sensitive bacilli gradually lose the lysogenic property which they acquired under special conditions, but the very resistant bacilli never acquire that property. It is conceivable that the resistant strains are responsible for the untoward outcome of disease in human beings. Theoretically the administration of lytic fluid should rid the intestinal tract of most of the infecting bacilli, and only if completely resistant bacilli in large numbers remain unacted on is the outcome of the disease a fatal one.

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**Hypochlorite Process of Oyster Purification.**—CARMELIA, (*Public Health Reports*, 1921, xxxvi, 876) reviews the results of experiments on a commercial scale, having for their object the purification of oysters polluted by sewage. The oysters are treated by two changes of chlorinated water covering a total period of from eighteen to twenty-four hours. The chemical practically sterilizes the water in which the oysters are floated and results in such marked bacteriological improvement in the bivalves that they may be regarded as safe for food, unless the initial pollution has been excessive. It is suggested by the writer that oysters, regardless of origin, might safely be treated in this manner.

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ORIGINAL ARTICLES.

RELATION OF ALEUKEMIC LEUKEMIA, SO-CALLED PSEUDO-  
LEUKEMIA AND MALIGNANT GRANULOMA.

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THERE is perhaps no more unsatisfactorily classified subject in the scope of the medical sciences than the enlargements of lymphatic nodes, or the hyperplasias of allied tissues, in the absence of a definite increase of circulating leukocytes. These diseases have been subjected to intensive investigation rather spasmodically during the past fifty years, but recently a generally heightened interest has been evident. This may be due to the fact that these diseases have increased in incidence—more cases have been seen in the University Hospital in recent years—the stimulation of investigation originating from certain bacteriologic findings in lymphogranuloma and the newer work upon the reaction of lymphatic organs to light rays. Increased clinical experience has, however, demanded a classification which will fit in with clinical course, reaction to roentgen-ray treatment and probable result from such treatment.

This laboratory and clinic have joined in the study of the whole subject of leukemic and aleukemic adenopathy for several years, a coöperation which has brought to light several interesting cases and a few profitable facts. The present paper puts on record three cases, grouped by their age, clinical course, physical appearance and somewhat by their pathology, which were diagnosed as Hodgkin's disease at first, but by close clinical analysis were removed from this category, and by the examination of excised glands were placed among the tumors and leukemias, or so-called pseudoleukemia.



The term "pseudoleukemia" was coined by Cohnheim in 1865 to describe a case of generalized lymph-gland enlargement without a leukemic blood picture. Since Cohnheim's time the term has been misused by very many writers. In a very cursory examination of the literature for this purpose, including the International List of the Causes of Death, we have found nineteen names purporting to cover his conception. More than that it became the custom in Europe before Sternberg's publications in 1898 and 1905 to speak of nearly all lymph-gland tumors as pseudoleukemia, and the term was, in certain quarters, synonymous with Hodgkin's disease.

Despite Turk's request of 1899, Sternberg's presentation before the German Pathological Society in 1912 and Symmers's article in 1909, this synonymous use of the term for Hodgkin's disease has persisted in literature. Sufficient evidence, however, is at hand to warrant the discontinuation of the use of the term in Hodgkin's disease and is rapidly accumulating against its application to the aleukemic stages or forms of leukemia. Sternberg does not believe it necessary. Pathologically speaking—and it is upon bioscopic and necroscopic glandular pathology that one should base a diagnosis—there seems little justification to apply the term "false leukemia" to the aleukemic stages of leukemia. Sternberg's grouping of Banti's disease under this title has more justification than the inclusion of more definite glandular or myeloid pictures. This, however, is not our present problem. We believe that this term "pseudoleukemia" should be used in an adjectival sense only and that there are adequate names and pictures for the groups to which it has been collectively applied. Thus, for example, the following cases, while not presenting a typical leukemic blood picture, have some evidence of lymphoid-cell production and a type of adenopathy consistent with general diseases of the lymphatic system. Such a clinical state hardly needs the name false leukemia, especially when a gland removed during life showed lymphoid hyperplasia of the leukemic type.

CASE I.—S. O., aged sixty years, m., w., s. Admitted to the University Hospital, December 4, 1920, complaining of swelling of the neck, axilla and groins. Had been in good health until April, 1919, when he noted a small swelling in the right axilla. A mass appeared a month later in the left submaxillary region. These masses probably increased but gave no trouble. In December, 1919, he began to have dyspnea, especially at night. The tonsils were then discovered to be large and diseased and were removed December 23, 1919. This removal cured his dyspneic symptoms. When the glands were first noticed the patient believes that his voice became weaker, although at times it seemed normal. The patient was in good condition, without much change in glands, until June, 1920, when after a slight cold masses began to enlarge. All his teeth except eight front lower teeth were removed, after which

some of the glands decreased somewhat. He remained in fair condition, but noted that he was tired and was going down hill when he was admitted in December, 1920. Lost twenty pounds in two years.

The previous medical history shows diseases of childhood with permanent impairment of hearing due to scarlatina. Had pneumonia when young and again when sixteen. Social and family history are negative.

Physical examination showed a well-nourished man with soft dry skin except over the knees and elbows, where it was wrinkled and harsh. The neck was the same width as the head, due to enlargement of lymph nodes. The mouth and pharyngeal cavity were negative. The remaining teeth were in fair condition. The pharynx and the remaining lymphadenoid tissue were congested. The neck, both anteriorly and posteriorly, showed irregular masses from pea to egg size, discrete, sharply outlined, freely movable, not adherent to skin. The thyroid was not enlarged; there was no tracheal tug. Chest emphysematous. Several masses under the skin similar to those in the neck. The axillary fossæ were filled with enlarged masses like in the neck. Lungs were negative. Heart area was enlarged to the left in the second interspace. L. B., 13 cm.; R. B., 3.5 cm.; L. O., 16 cm.; R. O., 9. cm.; in the first interspace, 8 cm. wide. There was some peripheral arteriosclerosis. Blood-pressure, 140-90.

The abdomen had a fatty flaccid wall except the upper section of the recti, which was resistant, and gave the impression of a mass beneath. The liver extended from the fourth costal space to the rib margin. The spleen was not palpable. The inguinal glands were enlarged like those in the axilla. The right epitrochlear gland was palpable. The patient was allowed to go out for a couple of weeks to return for roentgen-ray treatment. He worked rather hard and there was an enlargement in his glands during his absence. Before his temporary discharge a gland was removed under local anesthesia and was diagnosed as leukemic hyperplasia and not Hodgkin's disease, which was the preliminary diagnosis. The patient received very little treatment aside from the roentgen-ray, sodium cacodylate,  $\frac{1}{4}$  grain, being the only important measure used during his twelve days of treatment. There was a slight decrease in the size of the glands, but they did not become firmer. Following exposure while going to the roentgen-ray he developed lobar pneumonia at the left base and died. Before the development of this infection his temperature had ranged between 97° and 99° F., with a relatively higher pulse and respiration rate. During the pneumonia the rates were proportionate. The urine had shown a specific gravity from 1016 to 1020, with a constant trace of albumin and a few hyaline and light granular casts. Intake and output were proportionate. The phthalein elimination was 60 per cent. The skin tests for tuberculosis were negative. The Wassermann was negative.

# Blood counts:

Hgb.	R.B.C.	W.B.C.	P.	L.	M.	Tr.	E.	B.
88	4,670,000	5900	54	38	6	1	4	
93	5,400,000	6500	52	40	3	3	1	1

# Roentgen-ray started:

87	4,300,000	5900	56	37	5	2		
85	4,450,000	6100	74	20	3	3		
		3300	64	33	1	2		
92	4,700,000	6600	56	36	4	2	..	2

# Pneumonia:

85	4,400,000	6100	74	20	3	3		
		3300	64	33	1	2		

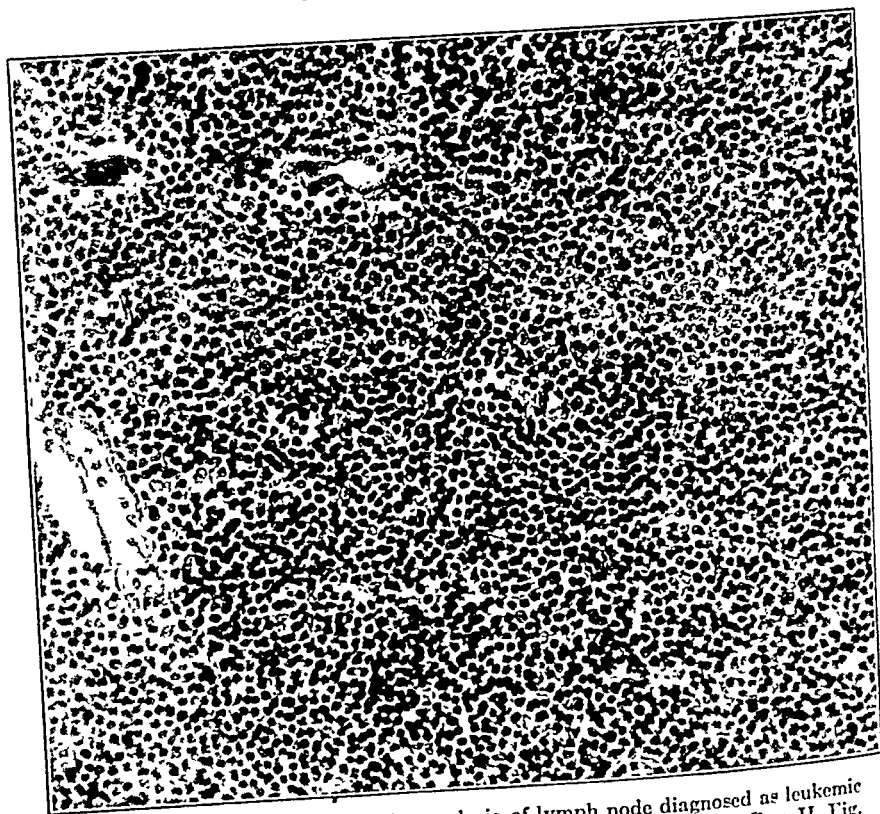


FIG. 1.—552. S. O. Uniform hyperplasia of lymph node diagnosed as leukemic hyperplasia; case aleukemic. Cells 7 to 10 microns. Compare with Case II, Fig. II, and A. H., Fig. IV, but contrast with A. E., lymphogranuloma, Fig. III.

A gland from the neck was about 2.5 x 2 cm. The smooth pale pink capsule is thin and uniform on section. The mass is pale, gray-pink, homogeneous, soft and not traversed by fibrous bands. Section (Fig. 1) consists of a rather uniformly staining mass fairly well outlined by a delicate capsule, outside of and within the splits of which are cellular infiltrates. The marginal sinus cannot be recog-

nized but the arrangement of some of these infiltrates raised the question as to occupation of what was the marginal sinus. The tissue cannot be recognized as lymph node. It seems to be made of a single type of cell separated by a few delicate connective-tissue strands carrying bloodvessels and cut at different angles. The cells vary from 7 to 11 microns, the nuclei from 5 to 9 microns. The nuclei are fairly well stained and have a clear but delicate nuclear network. The protoplasm is neutrophilic with here and there a slightly oxyphilic example. They are mostly round or elliptical, but some compressed ones are seen. Here and there one will see what seem to be a true young connective-tissue nucleus.

By Van Gieson the capsule and delicate septa show clearly, but there are no fibers between the cells.

A polychrome stain (only fairly satisfactory) shows no true granules of the myeloid type, but here and there one finds pictures like azure granules. By this stain a polynuclear eosinophile was seen and large mononuclears of large endotheliocyte proportions were found, and these have distinct vesicular nuclei and a purple cytoplasm, very distinct from the scanty neutrophilic protoplasm of the average cell of the section. One eosinophilic mononuclear was found.

The Schridde stain reveals no real perinuclear granules. Here and there one sees masses of irregular staining and granulated appearance and also masses of matter which might correspond to the above-mentioned azure granules. Section shows no oxidase granules by Graham's method.

*Clinical Diagnosis.* Aleukemic lymphatic leukemia.

*Bacteriologic Diagnosis.* Cultures: Heart blood; mesenteric lymph node negative.

#### POSTMORTEM.

##### *Gross Anatomical Diagnosis.*

Lymphatic leukemia.

Aorta: Early atheroma.

Heart: Dilatation; fibrosis of the myocardium; subacute verrucose endocarditis of mitral valve.

Left lung: Acute fibrinous pleurisy; lobar pneumonia; beginning consolidation of the lower lobe.

Right lung: Obliterative pleurisy; hypostatic congestion and edema.

Spleen: Lymphatic leukemia.

Stomach: Congestion and submucous hemorrhages.

Liver: Lymphoid infiltration.

Leukemic tumor of retroperitoneal tissue.

Kidneys: Slight chronic interstitial nephritis; cloudy swelling.

Bladder: Distention.

Pancreas:

Lymph node:

##### *Histological Diagnosis.*

Old healed myocarditis; acute infectious mitral valvulitis with vegetation.

Croupous pneumonia.

Hemorrhage.

Endothelial and lymphoid hyperplasia; congestion.

Petechial hemorrhages.

Lymphoid infiltration; cloudy swelling; fatty infiltration.

Chronic interstitial nephritis; cloudy swelling; lymphoid infiltration.

Normal.

Lymphatic leukemia.

**EXTERNAL EXAMINATION.** Autopsy one hour after death. Body of white male, aged fifty-eight years, looks not over fifty; 172 cm. in length, weighing about 160 pounds; of normal framework and good nutrition. Rigor not yet established; *livor mortis* present. Skin is smooth except for a slight healed scar over the left mandible. There is general glandular enlargement, involving especially the auricular, maxillary, cervical, axillary and inguinal nodes. These are soft and feel distinct. The skull is normal. The pupils equal and regular. The scleræ are clear. The nose and ears are negative. Many teeth are missing. The neck appears fat. The thorax is well developed. The genitalia are normal. A number of spots are seen about the right nipple, suggesting puncture wounds. The extremities are negative and the hair distribution is normal.

**INTERNAL EXAMINATION.** *Thorax.* The left pleural cavity is free from adhesions and fluid. The right pleural cavity is obliterated by dense adhesions. The pericardial sac is normal.

*Aorta.* The aorta is of normal caliber and shows numerous gray-yellow plaques in all portions.

*Heart.* Weighs 300 gm.; the epicardium is smooth without excess of fat. The organ is firm. The myocardium is dark brown with fibrous streaks. The papillary muscles and the chordæ tendineæ are normal. The mural endocardium everywhere is thin and smooth. The bases of the aortic cusps are slightly stiffened. On the auricular surface of the mitral valve is a group of small, rather soft, wart-like, yellowish growths. Other leaflets are delicate. The wall of the left ventricle is 16 mm.; right, 3 mm. The aortic orifices, 7 cm. Both ventricles are moderately dilated. The coronary artery is not sclerosed. The trachea and bronchi show no changes. The mediastinal lymph nodes are much enlarged, gray, soft and discrete.

*Left Lung.* Weighs 900 gm.; upper lobe is consolidated, except for the anterior margin. The lower lobe is crepitant, except for a small area posteriorly. The pleura of the upper lobe is covered with a little fresh fibrin. There are no apical scars. The cut surface of the upper lobe is gray, granular, slightly moist and airless; of the lower lobe red and moist; air can be expressed, except in a small patch posteriorly; bits of tissue of this area float in water. The peribronchial lymph nodes resemble those already described.

*Right Lung.* Weighs 500 gm.; normally collapsed. Cut surface is red and moist, and contains air, except for a dark red, hemorrhagic-looking area in the posterior part of the lower lobe. Pieces from this sink in water.

*Abdomen.* The abdominal fat, 1½ cm., flabby and moist looking. Muscles flabby, and this is true of the general musculature. The peritoneum is smooth, glistening and free from adhesions. There is no fluid in the peritoneal cavity. The bladder is much distended. The diaphragm reaches the fourth rib on the right side and the fifth on the left.

*Spleen.* Weighs 280 gm.; firm and capsule is smooth. The cut surface is dark red; the trabeculae are indistinct. The follicles are greatly enlarged and white. There are several larger white areas about 3 mm. in diameter.

*Stomach.* The stomach is moderately distended. The mucosa is normally rugous, showing numerous petechial hemorrhages.

*Intestine.* The intestine is negative. The bile passages are patulous.

*Liver.* The liver was not weighed, but probably weighed about 2000 gm., 29 x 23 x 10 cm., and of normal consistency. The lower border is somewhat rounded. The capsule is transparent. The cut surface is gray with distinct red centers of lobules; the surface is even.

*Pancreas.* Is small, of normal consistency and normally lobulated. Close to the pancreas is a tumor-like mass, 13½ cm. in greatest dimension. This is encephaloid, gray but not lobulated. Besides the main mass are many small, similar nodes, apparently enlarged lymph glands. Similar brain-like tissue is found along the abdominal aorta, forming practically a sheet of new growth throughout the retroperitoneal tissue. This growth is lobulated, and similar to glands of the neck, which had been exposed to roentgen-ray treatment.

*Left Kidney.* Weighs 230 gm.; 14 x 6 x 5 cm.; of normal consistency. Capsule strips with difficulty, leaving a pink, granular surface with a few scars. The cut surface is generally gray with bulging edges. Cortical striations are indistinct; those of the medulla appear normal. The glomeruli are of usual size. The pelvis is distended. The peripelvic fat is moderately increased.

*Right Kidney.* Weighs 170 gm.; 14 x 5 x 5 cm.; cortex, 7 mm.; medulla, 15 mm.; otherwise resembles its fellow.

The vertebral column, ureters, urinary bladder, prostate, seminal vesicles and psoas muscle are negative.

Notes: The bone-marrow of the shaft of the femur is red; that of the ribs shows no changes.

**MICROSCOPICAL.** *Heart.* The epicardium is of the usual thickness but shows no vascular or other changes. The endocardium is not shown. The myocardium shows very extensive replacement of the muscle, with fibrous tissue of adult type, in the midst of which, here and there, muscle fibers persist. From this last point and from the irregular outline the lesion appears not to be a healed infarct. There is no cellular infiltration or vascular change. Uninvolved muscle fibers are of the usual size, with preserved cross-striations, well-staining nuclei and inconspicuous peripolar pigment. The second section is from the mitral valve. The tissue consists of adult connective-tissue without bloodvessels, except in one area in which there are leukocytes and mononuclear cells. On the surface of the leaflet, corresponding to this area of infiltration, is a hyaline blood-clot in which are numerous areas of softening containing innumerable bacteria. The edge of the clot blends with the margin of the leaflet.

There is no apparent invasion of the leaflet by bacteria, nor any organization of the clot.

*Left Lung.* The pleura is much thickened with adult fibrous tissue, the superficial layer being heavily infiltrated with lymphocytes. The pulmonary tissue is uniformly consolidated, the exudate consisting of fibrin, leukocytes and with vast numbers of bacteria and a few red cells. Capillaries are compressed by the exudate. The interstitial tissue and vessels show no change.

*Right Lung.* The pleura is absent. The pulmonary tissue is uniformly consolidated with red blood cells, with which are a few leukocytes but no fibrin. Alveolar walls, capillaries and interstitial tissues show no changes.

*Spleen.* Capsule and trabeculae are normal. Follicles are greatly enlarged, with hyperplasia of lymphoid cells and the presence of coarse reticulum. The pulp is very bloody. There is one area of extensive endothelial hyperplasia. These endothelial cells are supported on a rather coarse reticulum, and are mixed with lymphocytes and leukocytes. There is not, however, diffuse endothelial hyperplasia through the pulp.

*Stomach.* Only mucosa and submucosa are shown. The former shows many hemorrhagic points but no exudative features.

*Liver.* The capsule is normal. Extensive lymphoid infiltration is found in the perilobular tissue, which is greatly widened; in these areas the bile ducts appear to be increased numerically. The liver cells are large, crowding the capillaries; they are granular, and nuclei often are poorly seen. Many rather small vacuoles are present, becoming rather large in the peripheral zone. The central veins are not distended. No fibrosis is seen.

*Pancreas.* The interstitial tissue is normal, as are the vessels and the ducts. The islets are numerous and large; the acini show no changes.

*Kidney.* The capsule is infiltrated with lymphoid cells. The interstitial tissue is much increased as streaks in the cortex, associated with hyalinization of many glomeruli and compression of tubules. Elsewhere tubules are of full size, with somewhat swollen, ragged and granular cells, in which nuclei are faint. No definite vascular lesions are seen, except for perivascular lymphoid infiltration.

*Lymph Node.* Follicles and sinus arrangement are completely obliterated. The structure consists of lymphoid cells supported on a reticulum.

There are numerous small bloodvessels. This tissue freely extends beyond the capsule.

Two additional sections show the same feature, with infiltration of the capsule by lymphoid cells.

CASE II.—J. M., aged sixty-one years, w., m., s. Admitted to the University Hospital for nodules on each side of the neck, in the axilla and in the inguinal regions. He has been in fair health until two years ago, when he noticed the small lumps on the right side of the neck about the size of a pea, which were followed by others. These were firm, discrete and without discomfort. They grew steadily, and two months later similar masses appeared in the axillæ and the groins. They were all of the same character. Has had some carious teeth but paid no attention to them. No loss of weight and no history pointing to any organic lesion. His previous medical history was negative until he had influenza, September, 1918, at which time the masses in the neck increased in size. In December, 1919, he had a second attack of influenza, with intestinal symptoms. On January 20, 1920, had acute pleurisy, after which he did not work until his admission to the hospital in March, 1920. The latter illnesses had no effect on the glands. He was a ship and stationary engineer. His personal and family history are negative.

A physical examination in the hospital shows a well-developed large male, tending to fatness, and appearing well except for the general adenopathy. Blood-pressure, 122-90. The teeth are dirty and carious, and considerable pyorrhea exists. Has some chronic pharyngitis. The neck is short and thick, with bilateral swellings from the jaw to the clavicle anteriorly and posteriorly. The masses vary greatly in size, pea to walnut—discrete, freely movable, firm, smooth but not tender or painful. No adhesion to the skin. No tracheal tug. The chest is large and emphysematous. Glandular masses are found below the clavicle and extending in the anterior axillary region. The left chest is more prominent than the right, the expansion being limited on both sides; the percussion note is slightly impaired over the whole upper chest anteriorly and posteriorly. The breath sounds in this area are coarse and loud; there is a friction rub on the left base posteriorly. There are glandular masses above the spine of the scapulæ. The heart apex-beat is not seen or felt. The supracardiac dulness at the first interspace is 8 cm., second 6.5 cm., left base 12 cm.; right base 4 cm.; L. O., 20 cm.; R. O., 17 cm. The heart sounds are negative. The abdomen is full. Liver dulness over the sixth rib. The spleen comes below the costal margin only upon inspiration. Throughout the abdomen one gets the impression of numerous small masses beneath the skin or the abdominal wall. On the left side below the spleen and almost to the groin there is a resilient mass deep in the abdomen, probably retroperitoneal. On the right side there is definite resistance but no definite mass. Marked adenopathy in both axillæ, especially along the axillary folds, the individual ones being larger than in the neck. Masses in the groins are similar. No edema of extremities.

A gland was removed and diagnosed as not Hodgkin's disease or tuberculosis, but either sarcoma or leukemia, of which the latter



was more probable because of the absence of intercellular fibers. The patient after exposure developed a lobar pneumonia of the right base and died. An autopsy was not permitted. The urinary examination showed the specific gravity ranging between 1020 and 1024, and an almost constant trace of albumin but no casts. The phthalein elimination was 55 per cent. The blood Wassermann was negative.

Blood counts:

Hgb.	R.B.C.	W.B.C.	P.	Small.	M.	Tr.	E.
82	4,800,000	13,800	43	36	11	7	3
	4,810,000	28,800	77	16	6	1	

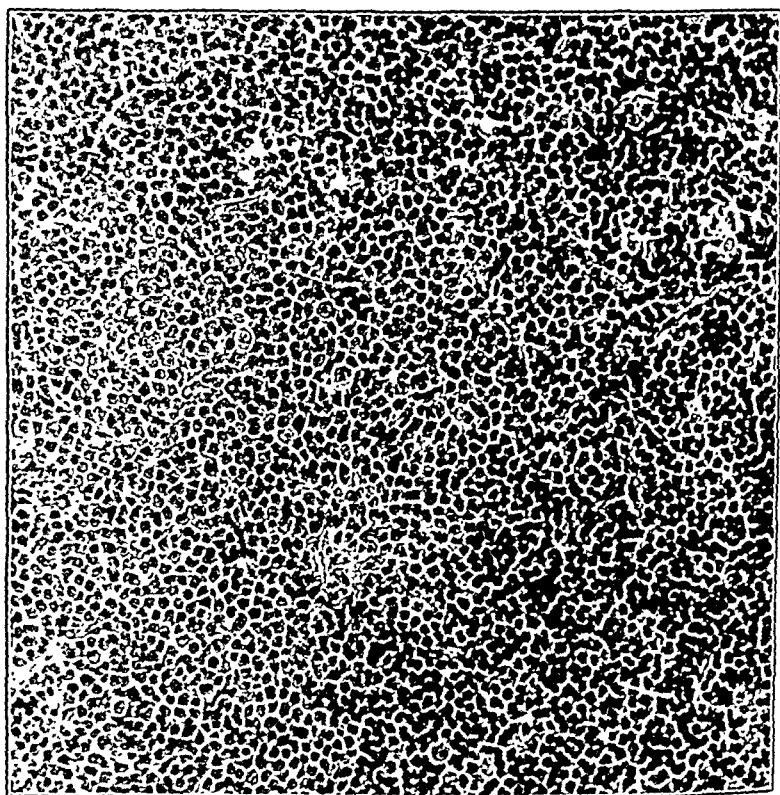


FIG. 2.—442. J. M. Uniform hyperplasia of lymph node without leukemia. Cells of 7 microns. Deeply staining nucleus. Diagnosed as aleukemic leukemia. Compare with Fig. I, Case I, and with A. H., Fig. IV, but contrast with Fig. III, A. E., lymphogranuloma.

The temperature ranged between 98° and 99° F. until the pneumonia developed, after which it developed 103° F.

Further detailed study of the excised gland revealed the following (Fig. 2): The specimen consists of a well-outlined cellular mass which cannot be positively recognized as a lymph node. The capsule is made up of dense fibers, a few long pale nuclei, and in the rifts

columns of adult lymphocytes may be seen. The position of the marginal sinus is sometimes indicated by a rift containing a few pale cells and a few lymphocytes. Trabeculae do not exist as in the normal gland. There are small irregular septa carrying bloodvessels. The extreme border under the capsule consists of small lymphocytes, of about 7 microns, rather uniformly packed. Between these cells, here and there, is a slightly swollen reticulum cell or a delicate connective-tissue septum. As one goes inward toward the center

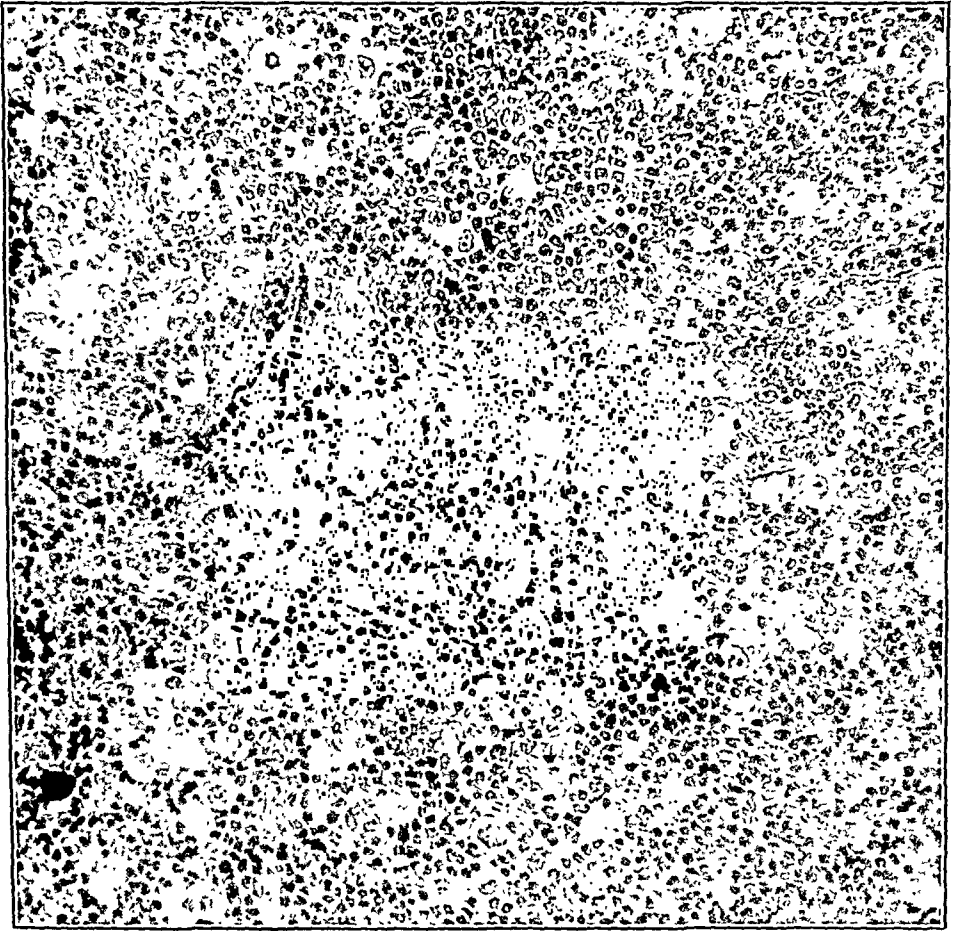


FIG. 3.—514. A. E. Hodgkin's disease in the cellular stage, six months' duration. Active process but the patient in reasonable good health and doing well under treatment.

of the mass the cells retain their rather uniform solid closely packed arrangement and incomplete separation by stroma but become distinctly larger. Under magnification of 1200 they are found to consist of a nucleus with a moderately coarse skein, a nucleolus or two nucleoli, sharply outlined, and a small amount of granuloid neutrophilic protoplasm. Mitoses, apparently normal in character, are common.

By Van Gieson there is no stroma except the well-formed adult

septa mentioned above. No endothelial, plasma, mast, eosinophile, neutrophile or giant cells. No fibrin, necroses, tubercles or pigment. The predominating type of cells is similar to some of the promyelocytes.

The Schridde stain fails to show any granulation in the protoplasm of the cells of this mass.

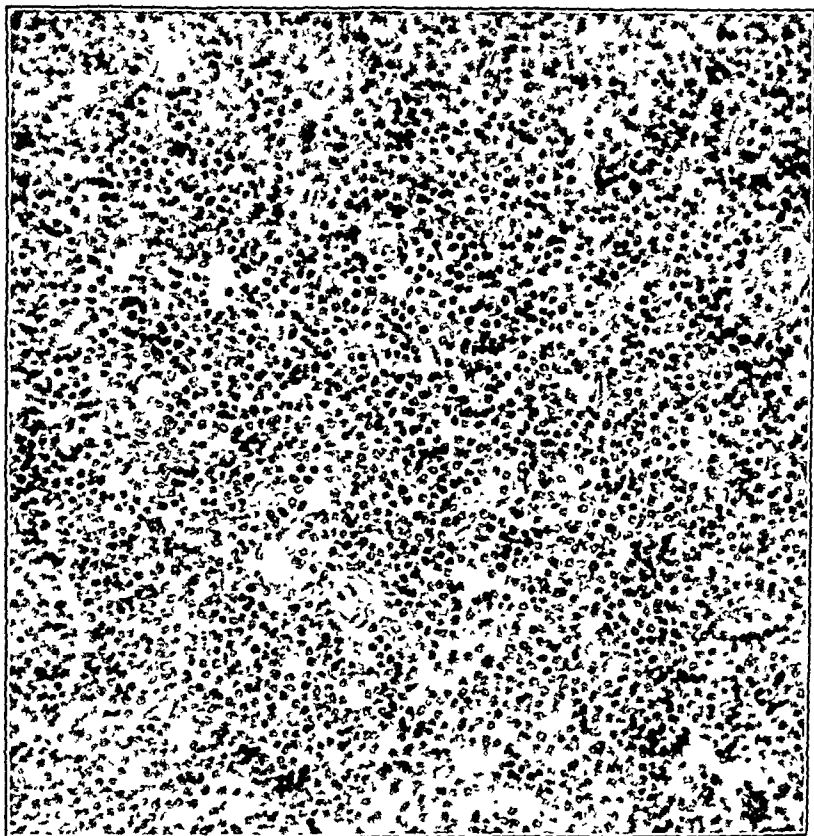


FIG. 4.—402-2 A. H. Axillary lymph node from a case of chronic lymphatic leukemia dying from pneumonia. Loose hyperplasia with much vascularization. Cells 7 to 8 microns.

CASE III.—S. J. M., aged sixty-one years, m., w. Admitted to the University Hospital February 14, 1914, complaining of swellings under the arms and in the neck and dyspnea. The patient has been in generally good health until six months ago, except four years before admission he had a swelling about the right elbow; this disappeared. Six months ago a lump appeared in the right axilla, which grew rapidly and became tender. Three months ago he had a swelling in the neck. He had a similar swelling on the left side. These swellings are slightly painful, sometimes extending down the arm, which is swollen; they are somewhat tender and have fluctuated in size. Sometimes one mass will enlarge while the other is

smaller. None has broken down. Five months ago the patient began to have dyspnea and swelling of the feet; has had some palpitation, also dull pain across the chest, especially in the right mammary region. Had nocturia for three years. Had a chronic cough for fifteen years. When the glands first appeared he lost fifteen pounds, but since has gained and is now twenty-five pounds above weight.

The medical and social history are negative. His wife died of tuberculosis sixteen years ago.

The physical examination shows a heavily built, fat, florid, slightly dyspneic man between fifty and sixty. The muscles are flabby, the skin is warm and slightly yellowish. The superficial glands seem enlarged—solid, conglomerate and tender. They are fixed to the fascia but not to the skin. The axillary are most markedly involved, those in the neck and groins being smaller and more separate. The head and eyes are negative. The teeth are badly decayed and worn down; some pyorrhea. The thorax is heavy. The right mammary and pectoral regions are indurated and tender with discolored skin over them. There is some impairment of resonance and bronchovesicular breathing at both apices anteriorly. Impairment of resonance and breath sounds over the whole right chest posteriorly. The apex impulse is not found. L. B., 13 cm., R. B., 5 cm.; L. O., 17 cm.; R. O., 15 cm. A blowing systolic murmur is heard at the apex and in the left axilla. The abdomen is large and pendulous. Liver 4 cm. below the umbilicus. The spleen is not felt. The extremities are negative except for a slight edema. The patient remained in this condition for several days, when he suddenly became toxemic and died in three days. For five days after admission he had run a temperature from normal to 101° F. It then settled to an irregular form, 97° to 100° F, with a disproportionately high pulse and respiration, and then continued until his toxemia appeared, when it became very irregular and up to 105°. A gland was removed and diagnosed as sarcoma, with reservation. The urine showed specific gravity of 1025, with a constant trace of albumin, and light granular casts. The Wassermann and von Pirquet were negative. A blood culture during the toxemic stage showed pneumococcus.

#### Blood picture:

Hgb.	R.B.C.	W.B.C.	P.	L	M.	Tr.	E.	B.
86	4,400,000	9800	86	11	2			
84	4,900,000	9000	75	23	2			
89	5,100,000	22000	86	17	3	3	1	

A gland was excised during the treatment. No attempt was made to diagnose the original site of the growth, and at autopsy such an attempt failed.

*Excised Gland.* The material consists of several small fibrocellular pieces. The mass cannot be recognized as a lymph node. It has probably been partly encapsulated and spread out into and through the capsule. The capsule is wide, rather acellular; in its outer two-thirds it is adult fibrous tissue. The inner part is actively

growing and consists chiefly of large elliptical or elongated, palely staining connective-tissue cells with a few small mononuclears, here and there a plasma cell, numerous in bloodvessels, a few free red blood cells—in other words, fairly active granulation tissue. There are rifts in and under the capsule filled with large cells to be described later. The majority of the mass consists of eosin-stained cell shadows and some better retained areas, with indefinitely stained basophilic nuclei. The center is difficult to describe and determine, but apparently the further one goes from the capsule the more there is disintegration; the remnants of fibers and long slender nuclei are to be seen irregularly scattered through the mass. It has apparently been very bloody, because there are some spaces filled with red blood cells apparently without wall and a few degenerated capillaries are seen. The cellular nests in the capsule consist of well-outlined groups of large cells with large well-outlined round elliptical and lobed nuclei and a small amount slightly granular or vacuolated protoplasm. There are sometimes several nuclei. The mitoses are moderately active. Red blood cells are numerous between these large cells. There are occasional polymorphous neutrophiles and eosinophiles. The cells of the central necrotic mass seem to have been the same kind of cells. Within the mass there are no lymphocytes and no endothelial, plasma or mast cells; a very vague reticulum is seen by Van Gieson; there are no eosinophiles; no myeloid or giant cells; no tubercles or pigment.

#### POSTMORTEM.

##### *Gross Anatomical Diagnosis.*

Lymphadenitis of the axillary, subclavicular, subclavian, submaxillary and mediastinal lymph nodes.

Lung: Pleural effusion; healed pulmonary tuberculosis.

Heart: Pericardial effusion; fatty infiltration of the epicardium; cardiac hypertrophy; chronic fibrous aortic and mitral valvulitis; tricuspid and pulmonary insufficiency; right dilatation; chronic fibrous myocarditis; brown atrophy.

Liver: Cloudy swelling and fatty degeneration.

Spleen. Chronic fibrous and calcareous capsular splenitis, with softening of the organ.

Adrenals: Softening.

Kidney: Chronic parenchymatous nephritis.

Stomach: Atrophic catarrhal gastritis. Fibrous and fatty endoaortitis of the aorta.

Pancreas:

Intestine: Meckel's diverticulum.

##### *Histological Diagnosis.*

Large round-cell sarcoma resembling lymph-node endothelioma.

Emphysema, with secondary compression; atelectasis; passive congestion and chronic interstitial pneumonitis; chronic catarrhal bronchitis.

Chronic interstitial mural endocarditis; coronary sclerosis, with hypertrophy and secondary brown atrophy.

Passive congestion with parenchymatous degeneration and fatty metamorphosis.

Chronic fibrous capsulitis.

Congestion and cloudy swelling.

Chronic fibrous and fatty endarteritis.

Atrophy, with replacement by fat.

*Bacteriological Diagnosis.* Streptococcus in cultures from heart blood, lung, spleen, liver, kidney and lymph nodes of the neck.

**GENERAL.** The body is that of an adult white male, aged fifty-five years; five feet eight inches tall; weighs about 200 pounds; is broad and thick-set, with a tendency to obesity; gray hair; blue eyes. The pupils are moderately dilated; the conjunctiva is muddy. Mouth: Teeth are in bad condition, especially the upper jaw, where only a few decayed ends are present. Mucous membranes are pallid. Both sides of the neck are swollen. Upon palpation the swelling is apparently in the cellular tissue as well as in the glands. There is a short, recently healed incision beneath the right ear. Rigor mortis is marked. Livor mortis in the dependent positions is marked over the anterior chest and over the neck. The tissues of both axillæ, but more especially the right side and the right flank, are boggy. There are well-marked palpable masses confined to the right axilla.

On primary incision the panniculus is found to be moderate; the musculature is fairly well developed. The axillary space was dissected out and contains an infiltrating mass of lymph nodes. These lymph nodes vary in size upon section from 4 cm. to 1 cm. They tend to run together, but the larger ones are sharply defined. Upon section they have a fleshy, firm appearance while some of the smaller ones have undergone a yellowish softening, which is comparable exactly in appearance to that of a mushroom which has its outer covering stripped off. Along the fascia of the pectoral muscle on the right side are numerous small bodies 0.5 cm. long, firm and fleshy; these do not infiltrate the muscle but seem to run somewhat into the fatty tissue over the pectoral fascia. This condition is not noted on the left side. The same small bodies are noted deep in the axilla and along the neck. The glands of the neck are enlarged in the same fashion, and upon section show caseous centers.

*Abdomen.* The cavity contains no fluid and the epiploic appendages are prominent. The lower border of the liver is at the border of the ribs. The stomach is slightly distended below this. The transverse colon, freely movable, runs straight across the abdomen. The great omentum is filled with an excessive amount of fat.

*Liver.* Weighs 2100 gm.; it measures 29 x 19 x 11 cm.; is pallid upon the surface and the edges are rounded; cuts with a buttery resistance. The cut surface is pallid, and the lobules are poorly defined. About the vessels may be seen radiations considered as fibrous. Some grease may be scraped from the surface. The gall-bladder contains 30 cc of a very dark viscid bile. The bile ducts are patulous.

*Spleen.* Weighs 300 gm.; measures 13 x 9 x 6 cm.; the organ is soft; the capsule is distinctly thickened and calcareous in some parts. The cut surface of the pulp is soft and mushy; the trabeculæ are moderately prominent, as are also the follicles. The surface has a generally pallid appearance.

*Pancreas.* Measures 20 cm.; long and is somewhat thinner than usual. Upon section the lobules are small and sharply defined.

*Adrenals.* Are small, friable and removed with difficulty.

*Left Kidney.* Weighs 230 gm.; measures 13 x 5 x 5 cm.; the organ is firm, pale, blue and cuts with resistance. The cut surface bulges. The capsule strips without difficulty leaving a smooth surface. The entire kidney substance measures 2.5 cm.; cortex, 6 mm.; surface is pallid with granular reddish interlineations following the course of the bloodvessels throughout the cortex.

*Right Kidney.* Weighs 190 gm.; measures 11.5 x 4.5 x 2.5 cm.; entire kidney substance, 3.5 cm.; cortex, 7 mm.; corresponds in detail to its fellow.

*Bladder.* Contains 1 dram of a light amber urine, but otherwise is negative.

*Stomach.* Contains about 200 cc of a liquid greenish content; distended with gas; flattens out readily upon the table. The wall is somewhat thinner than usual; mucosal surface is granular and thin.

*Small Intestines.* Shows a Meckel's diverticulum, otherwise nothing to note.

*Thorax.* The left pleural cavity is free from fluid and adhesions. The right pleural cavity contains 1000 cc of a serous fluid, non-inflammatory.

*Right Lung.* Weighs 285 gm.; floats upon the fluid and is collapsed; when cut it presents the exact appearance of its fellow on the opposite side. The basal portion of this lung shows some firm stony bodies which upon section seem to have a caseous center. Upon section the smaller bronchi purulent material exuded from each.

*Left Lung.* Weighs 350 gm.; upon removal it collapses and crepitates with a doughy feel. A very small area at the base is somewhat darker, otherwise the surface is pale gray, smooth and glistening. The organ cuts with resistance simply because the lung is difficult to hold. The cut surface is gray and dry; at the base a small amount of fluid exudes. The mediastinal lymph nodes, bronchi and trachea were removed in one mass. The trachea has an excess of mucus; it is small and shows considerable injection.

*Heart.* Weighs 440 gm.; *in situ* widely dilated to the right. The organ is fairly firm; musculature shows some bronzing. Subepicardial fat is excessive in the usual situations. There are small epicardial plaques. The left ventricle is firm; the wall measures 2 cm.; the cavity is small. The aortic orifice measures 9 cm.; valve leaflets are thickened at the bases. The anterior leaflet in the sinuses of Valsalva has calcareous plaque-like thickenings. The mitral orifice measures 11 cm.; the valve leaflets are moderately thickened throughout, also toward the base. The chordæ tendinæ are lengthened, but are thick; papillary muscles are short and stocky. The heart cavities contain stratified chicken-fat clot. The

right ventricular wall measures 7 mm.; tricuspid orifice, 10 cm.; the valve leaflets are thin; pulmonary orifice measures 11 cm.; the valve leaflets are thin.

*Aorta.* Retains some of its elasticity; shows upon the intimal surface various yellowish platelets.

**MICROSCOPICAL.** *Lung.* The pleura on these sections is thin. The alveolar spaces have in one section become quite thin and stretched so that the spaces were dilated. Upon this, due to pressure of the pleural fluid the spaces were compressed so that now most of the section shows the wall in apposition. To overcome this the emphysema has remained in a compensatory way in other parts, mostly in the periphery of the lung. Congestion is quite marked, and this is probably passive in nature, due to large numbers of heart-failure cells. The bronchi have well-developed catarrhal effects, in that the epithelial cells were proliferated then swollen and many desquamated, so that the bronchial lumina are filled with mucus and débris. The bloodvessel walls are quite thick, owing to old fibrous tissue.

The second section has been taken from a point where pressure of the fluid was of longer duration. Here some cellular proliferation, with organization of fibrous tissue, is taking place in some of the walls of the compressed air spaces.

*Heart.* The epicardium on the section is thin. The subepicardial fat is moderate. The coronary vessels are quite thick and slightly congested. There is no increase to the connective tissue except about some of the vessels. The endocardium, however, is quite thick, showing penetration into the myocardium between the pectinate muscles. The myocardium shows evidences of an old hypertrophy, since here and there a clear division is well shown. At present an atrophy overshadows the increase in size. This is manifested by a thinning of the fibers with the deposition of considerable myohemoglobin at the poles of the nuclei. There are no marked degenerative features.

*Aorta.* Arteriosclerotic changes are moderate, mostly confined to the intima. The latter has many thickenings; loss of elastica is prominent; replacement by fibrous tissue with secondary hyalinization is confined to patches. Here also a patchy fatty change has taken place in the intima.

*Liver.* The capsule of Glisson is not thickened, although some cellular proliferation is to be seen in perilobular positions. No marked proliferation is present. The central lobular veins are slightly dilated and filled with red blood cells, which congestion extends into the capillaries. The liver cells show well-marked degenerative changes, more so about the central lobular veins. Here the cells are broken down, outlines poor, granular and filled with multiple small vacuoles. Many of those just about the rim contain fine brown granular pigment.



*Spleen.* The capsule is decidedly thickened and irregular. The trabeculae are not prominent. The bloodvessel walls show some hyaline change. The follicles are loose and open. The general splenic pulp is loose and the small cells are present without any definite hyperplasia. Congestion is moderate and there is no pigment.

*Pancreas.* There are no prominent fibrous-tissue changes. The parenchymal cells take the stain well and are compact. The islands of Langerhans are also small and compact. There has been some atrophy, as evidenced by replacement by a considerable amount of fat.

*Kidneys.* The capsule is not thickened, but in places there is some proliferation into the cortex. The fibrous tissue is not prominent, although very slightly increased. The bloodvessels are rather prominently congested. The glomerules are full; there is swelling due both to proliferation plus congestion and distention of spaces. The tubular cells are small and very granular, and their nuclei are sharp; granular casts predominate. The usual fibrous stroma is present in the medulla. The other section is like its fellow, except that degeneration of the cortical tubules is more prominent.

*Adrenals.* Capsule and fibrous tissue are not marked. The parenchymal cells are open and separated probably by fluid. The cells show both granules and vacuoles in equal number. Medullary congestion is moderate; chromophilic proliferation of medullary cells is not marked.

*Tumor.* Six slides taken from the tumor mass in the axilla, lymph nodes and pectoral muscle. The slides show the same type of tumor for all. The cell is a small round or oblong cell, with a small amount of acid-staining protoplasm and a large vesicular and hyperchromatic nucleus. It is larger than a lymphocyte and about the size of an endothelial cell. Grossly large degenerated areas are described. Microscopically these areas appear as coagulated and necrotic tumor cells which are swollen, diffusely acid staining, with complete loss of nuclei. In the active portion of the slides karyokinetic figures are well seen.

**BACTERIOLOGICAL EXAMINATION.** Tubercle bacilli were not found. Streptococcus was found in cultures from the heart blood, lung, spleen, liver, kidney and lymph nodes of the neck.

These three cases, while finally diagnosed in Case III as sarcoma and in the others as aleukemic leukemia, nevertheless present many features in common. They illustrate first how these cases may remain for many months without seriously disturbing the patient's general health, so that they are incorrectly diagnosed, or temporization is practised until the entire lymphatic system is involved beyond reasonable expectation of good result. All three cases died from intercurrent acute infection after a short and rather stormy course.

All of them were at first supposed to be Reéd-Hodgkin's disease, but certain clinical features stamped them as atypical if they were to be so classified. The ages—sixty, sixty-one and sixty-one—are twice the average of our own cases of lymphogranuloma. Cases I and II from the history showed that there had been an extensive involvement of the lymphatic apparatus from almost the very beginning. This was a point against the diagnosis of Hodgkin's disease, as it practically always begins as a localized process, and extends usually from one group to another until it has become more or less generalized. It is the exception rather than the rule for cases of Hodgkin's disease to show extensive involvement of all the superficial lymphatic groups. Theoretically it would eventually do so, but death usually frees the patient before this has occurred. On the other hand leukemia, both of the leukemic and aleukemic type, is essentially a general disease. One group of glands, it is true, may be much larger than another, but the enlargement of the whole system is always discoverable. In the ever-varying clinical manifestations of individual patients it may be difficult to establish with certainty that most or all lymph nodes became enlarged at or near the same time. The fact that the adenopathy is general is quite as important as the uniformity and synchronism of the enlargements. Patient history-taking and physical examination will aid greatly, but the histology of an excised gland will clinch the matter. This is illustrated in Case III, which was diagnosed by biopsy as sarcoma. There was no special involvement of the inguinal groups, and at postmortem there was none of the abdominal glands.

In comparing the three cases clinically at the very outset the chief complaint is enlightening. The patient whose case was diagnosed as sarcoma gave as his chief complaint, "Swelling under the arms and in the neck," while the two cases of aleukemic leukemia gave as their complaints, "Swelling in the armpits, the neck and the groins" and "Swelling on both sides of the neck, in the axillæ and in the inguinal regions," respectively.

The first patient complained of a more or less localized trouble and the other two of a pretty generalized process. This distribution was borne out upon physical examination, and in the latter cases should have led the clinician to consider the leukemias rather than Hodgkin's disease or lymphosarcoma.

The small tumors appearing early above the scapulæ in the leukemic cases are unusual and suggestive. This is a point clinically against Hodgkin's disease, for while such a distribution might be possible in this condition it is more common in leukemia.

We would like to emphasize for the leukemic cases the discrete nodules in the axillæ, firm, well-outlined, movable masses, not tending to coalesce, without pain or tenderness, yet distinctly tumorous as the patient was inspected.

In leukemia the individuality, the discreteness, of lymph nodes is

preserved, a condition the more readily appreciated if one consider the essence of the disease, a lymphatic hyperplasia, lacking the inflammatory character of lymphogranuloma and the disregard of the capsule by sarcoma. In Case III, however, the tumors, especially in the axillæ, were conglomerate and fixed to the subcutaneous tissue, somewhat painful and tender, with bronzing of the overlying skin, induration and some retraction of the nipple.

In many cases of Hodgkin's disease and of widespread extraneous tumors of the lymphatic apparatus other than the leukemias there occurs a reduction, in the differential count, of the mononuclear elements while the total count may remain normal or show a leukopenia. To state it figuratively there is a reduced output from the mononuclear factory because so much of it is not in working condition. This gives oftentimes an apparent polymorphonuclear leukocytosis. In the two cases of aleukemic leukemia the blood picture was as follows: The blood in Case I was at first sublymphemic, giving a count of 13,800, with small mononuclears at 36 per cent and large mononuclears at 18 per cent. Infection increased the total count and the polymorphonuclear neutrophilias. Case II had low normal total counts and very distinct lymphocytosis. On the other hand, Case III the sarcoma case, had neutrophile percentages of 86, 75 and 86, with total counts within normal limits.

In other words, from the standpoint of the clinician the two cases of aleukemic leukemia showed a blood picture which indicated activity of lymphoid tissue, a condition not found in lymphogranuloma or sarcoma.

The absence of actual leukemia does not exclude these cases from the leukemias, since Paltauf, Kundrat, Sternberg, Warthin, Fraenkel and others admit the fact that such cases may become frankly leukemic. Fraenkel maintains that if blood formulæ be followed carefully true leukemic phases may be discovered, and that he has repeatedly seen this happen shortly ante mortem.

The spleens of the two cases of aleukemic leukemia were slightly enlarged. One was found at autopsy in a state of active mononuclear hyperplasia.

There was in histological preparations from the autopsy of the first case general infiltration of organs with the mononuclear type cell and none at all in the third case. This probably more than any other feature stamps the first case as leukemia of the aleukemic type.

**Relation to Cellular Hodgkins.** Microscopically the pathological picture of aleukemic leukemia is widely separated from Hodgkin's disease. While the cellular type of the latter may approach the picture of uniformity of cell proliferation seen in aleukemic or leukemic growth, there are, however, always present the signs of inflammatory reaction; the large endothelioid cell and other chronic granulomatous elements are present to a greater or less extent in

every case. The picture seen in leukemia, with and without an increase of circulating leukocytes, is that of a uniform cellular hyperplasia, with little or no stroma and only occasional endothelial and reticulum cells. Incidental inflammation may add granulation tissue, or under roentgen-ray stimulation large endothelioid cells may become slightly more numerous, but they do not occur in groups and the development does not approach the picture of malignant granuloma in the formation of coarse fibrous reticulum. (Contrast Figs. 1, 2 and 4 with Fig. 3.)

Careful study of the cases, bearing in mind the features discussed above will greatly aid in an early diagnosis, but it would seem that a diagnostic excision of a lymph node is the best method of making a decision, an opinion also expressed by Harvier.\* Not only does this place a case in a definite group, but it gives the roentgenologist the necessary guide for treatment. This applies especially to Hodgkin's disease (lymphogranuloma malignum), which we have divided in our study into the cellular, the fibrocellular and the sclerosing varieties or stages, with the hope of learning something about the recognized fact that some cases do well with the roentgen-ray, others do badly, while still others do well for a short time only to have serious remissions. These varieties are due somewhat to the rate of growth or stages of the disease as Longcope points out, but it is to be hoped that such a working classification will in the future indicate some difference of virus or reaction of the patient. We are not now prepared to draw absolute conclusions, but it appears that in order of favorable response to roentgen-ray treatment the cases may be grouped first as most favorable, the cellular variety, second the fibrocellular and least favorable the sclerosing type. Perhaps our present information should only allow us to state that a case is favorable to the degree that it remains cellular in histology, unfavorable to the degree that it develops fibrous tumors.

The two cases of aleukemic leukemia are further interesting from the standpoint of treatment and prognosis. In Case II no treatment had been given but Case I was doing well in that no reactions had occurred, the gland masses were slightly smaller and the general health of the man was excellent. Since careful treatment of leukemic adenopathy offers definite hope in prolonging life at least, these cases should be diagnosed as early as possible, and this seems only practicable by adenectomy. We have discussed in a recent article the precautions to be used in selecting a gland for diagnostic excision.<sup>10</sup>

We wish to put on record a brief note of two attempts at further classification and diagnosis of these conditions that resulted negatively. Having seen that a very definitely different response to the rays was given by the cellular and fibrous groups of lymphogranu-

\* *La médecine*, 1920.

loma, it suggested itself to us that in the process of tissue destruction some specific protein might be formed and that some reactive substance might be elaborated. We were aware that the body does not produce antibodies against its own tissues, but we thought an antigen might be developed in glands under the roentgen-ray. We obtained by operation on Reed-Hodgkin's disease a large gland, from autopsy on S. O., a retroperitoneal mass, and by operation a sarcoma of the cervical glands. The first was ground in saline under sterile precautions and 0.3 per cent trikresol added. The other two were extracted according to the method of purifying proteins for skin sensitization tests. These substances served as antigen for skin tests upon the following cases:

Malignant granuloma—one case before and after roentgen-ray treatment; malignant granuloma—one case before roentgen-ray treatment; malignant granuloma—one case after roentgen-ray treatment; lymphatic leukemia—one case before and after roentgen-ray treatment.

All of these tests were negative.

**Summary.** 1. Two cases of aleukemic leukemia and one case of lymphosarcoma, similar, to some degree, in clinical course and physical appearance, and their distinction from lymphogranuloma, are reported.

2. Attention is called to the need for classification of the enlargement of lymphatic bodies and the hyperplasias of these and allied tissues in the absence of a definite increase in the circulating leukocytes.

3. The term "pseudoleukemia" has outlived its usefulness as a noun and should be used in an adjectival sense only.

4. Aleukemic leukemia is a systemic lymph-tissue disease, in pathology essentially like typical leukemia, but without increased circulating leukocytes. Leukemic phases may occur in its course or just ante mortem. (Compare Figs. 1, 2 and 4.)

5. A generalized lymphadenopathy is more suggestive of leukemia than of lymphogranuloma and tumors.

6. The two cases of aleukemic leukemia reported, while showing very extensive involvement of the lymphatic apparatus, gave no reduction of circulating mononuclears, a relative reduction being a picture usually seen in granulomata and sarcomata, involving much of the lymphatic apparatus. This point should be a decided help in clinical differential diagnosis.

7. Aleukemic leukemia is widely separated from cellular Hodgkin's disease in its histology by the absence of inflammatory changes in the former and their presence in the latter; leukemic processes are definitely more uniform or homogeneous than granulomatous.

8. An excision of a lymph node for microscopic study is the only reliable method of making a decision as to diagnosis in lymphatic enlargements. It is valuable also from the standpoint of prognosis and treatment.

9. Mention is made of a difference in the response to the roentgen-ray of the leukemic and the granuloma groups as seen in the affected lymph node. This will be taken up in a later communication.

10. An attempt at the production of an antigen for specific protein skin tests in the lymphatic diseases resulted negatively.

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### THE HEART IN INFECTIOUS DISEASE.<sup>1</sup>

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ONE of the most interesting and puzzling questions in the practice of medicine is the effect of infectious disease on the heart. Much unwarranted empiricism still exists in the treatment of the circulation during and after an infection. It is well now and again to pause and to take account of the progress of our knowledge of the influence of infectious disease on the heart and circulation. It is my desire to call attention to some of the known facts of this influence and to urge investigation of points that are in doubt. I shall take up in turn briefly the pathology, symptomatology and treatment of the heart in infectious disease.

In discussing the changes in the heart due to infections it is necessary to separate these infections into two groups: First there are those diseases which are quite likely to cause some permanent damage to the heart, and, second, there are infectious diseases in general which poison the heart temporarily but probably result in little or no permanent damage. In the former group are, in the first place, the infections of the rheumatic type—rheumatic fever, chorea, tonsillitis and scarlatina; secondly, there is diphtheria; thirdly, syphilis; and finally, the diseases, such as pneumonia, influenza and streptococcus septicemia, which may rarely attack the

<sup>1</sup> Read before the Section on General Medicine of the College of Physicians of Philadelphia, March 28, 1921.

heart directly. Temporary poisoning of the heart muscle may result from almost any disease—typhoid, pneumonia and so on.

Rheumatic fever and allied infections may attack and produce changes in endocardium, myocardium, and pericardium, any one, two, or even all three. A pancarditis is not uncommon. The typical lesion is the Aschoff body, or submiliary nodule, in the myocardium. Extensive involvement of the myocardium would result in considerable scarring so that permanent damage must always be suspected in the heart of any patient during or after illness belonging to this rheumatic group. The valves or pericardium give evidence of extensive cardiac involvement in rheumatic fever. Rarely if ever is the myocardium much damaged without evidence of endocardial or pericardial disease also, although transient heart-block may occur in rheumatic fever in hearts which do not show signs of valve changes or pericarditis. The occasional finding of acute heart-block should make one feel that any person who has suffered from rheumatic fever is not likely to have a perfectly normal heart even though it appears normal to auscultation and percussion.

Diphtheria toxin may produce serious and extensive necrosis of the myocardium, and here again it seems likely that any person who has been through a severe attack of diphtheria has a scarred heart. Heart-block, sometimes of very high grade, has long been known to occur in diphtheria. In my cardiac clinic are two cases of complete heart-block in young people whose past history is negative except for diphtheria. Not only may there be extensive auriculo-ventricular block, but also intraventricular block of bundle branch and arborization type may be found. How often such changes may occur transiently in diphtheria we are beginning to discover. Finally there is one other cardiac condition of great importance in diphtheria—that is, the sudden collapse with gallop rhythm, leading at times to sudden death and ascribed to cardiac nerve involvement (“disintegration of the vagus,” as Park calls it). This condition needs further study.

Syphilis affects the heart in two ways: either directly by gummatous invasion of the myocardium or by arteriosclerotic changes in the aorta and coronaries, or by both. Syphilitic aortitis is beginning to be regarded generally less as a disease entity and more as a condition associated with cardiac syphilis. In other words, one may speak rather of syphilitic heart disease with aortitis than of aortitis alone. There may be extensive syphilitic involvement of the bundle of His and its branches which yields to antisypilitic treatment, or there may be thromboses with scarring of the myocardium, perhaps leading to aneurysm of the heart itself and perforation of a ventricular wall. Any patient with chronic syphilis should have a careful investigation of heart and aorta made—by examination, roentgen ray and electrocardiogram. How early in the disease the heart may be attacked we are not yet sure. Undoubted cases of secondary syphilis

with cardiac involvement are on record, and Brooks<sup>2</sup> thinks that it may be common. At the Massachusetts General Hospital we have been examining secondary syphilitics from the cardiac standpoint, but as yet have failed to find out of a small number any giving signs or symptoms of cardiac involvement. It seems likely that such invasion may occur early in lues without any evidence.

Other rarer infectious causes of permanent damage in the heart are such diseases as pneumonia and typhoid fever. Rarely an endocarditis or a pericarditis may result from pneumonia, and the myocardium itself in fatal cases may show cloudy swelling and necrosis. Postmortem examination of typhoid fever hearts shows not infrequently mottling with marked parenchymatous degeneration microscopically. It is unlikely, however, that mild attacks of typhoid fever produce much change. The blood-vessels, both arteries and veins, may be considerably damaged in typhoid fever, and this disease has been included by some as a likely cause of arteriosclerosis. Other diseases such as influenza, gonorrheal septicemia and streptococcus infections may rarely result in endocarditis, pericarditis or perhaps myocarditis.

Now let us turn to infections as they affect the heart temporarily by poisoning. One of the most important papers of recent years is that of Newburgh and Porter.<sup>3</sup> They wrote as follows: "The experiments consist of four series of ten dogs each. In the first the normal ventricle was fed with normal blood; in the second the pneumonic ventricle was fed with normal blood; in the third the normal ventricle was fed with pneumonic blood; in the fourth the pneumonic ventricle was fed with pneumonic blood.

"It is very generally believed that the heart muscle is seriously injured in pneumonia and that heart failure from this source is a frequent cause of death in this infection.

"The experiments presented in this communication show that the cardiac ventricle from dogs that have died from pneumonia contracts as well as the ventricle from healthy dogs, provided the pneumonic muscle is fed with normal blood. When a normal ventricle is fed with pneumonic blood the contractions are much impaired. If, however, the ventricle from a dog with pneumonia is fed with pneumonic blood the contractions are almost normal in extent and may be normal in duration.

"Thus in pneumonia the heart muscle is essentially normal, whereas the pneumonic blood is distinctly poisonous to heart muscle suddenly fed with it. In the body, during the gradual course of the disease, the blood is progressively affected and the heart muscle gradually adjusts itself to the poison, with striking success."

The effects of poisoning of the heart resulting in functional

<sup>2</sup> Syphilis of the Heart. Read at a meeting of the Suffolk District Medical Society, Boston, December 29, 1920.

<sup>3</sup> Jour. Exper. Med., 1915, 22.



misleading. Signs already mentioned of actual heart involvement are of course much more important.

Finally, I shall say a few words about the treatment of the heart and the circulation in infectious disease. Such therapy may be divided into three groups in the order of their importance: First, specific treatment of disease is most important. Of course this is possible only in certain diseases, but in those it must be accomplished with wisdom. By so doing much heart disease can be avoided and the progress of that already begun stopped. This is particularly true of diphtheria with antitoxin, and syphilis with arsphenamine and mercury. In rheumatic fever I feel convinced that the salicylates act almost as a specific. Certainly when given early in the disease and pushed the infection can usually be stopped short and by so doing probably much heart disease averted. This is a very important measure to urge, I believe, in the prophylaxis of rheumatic heart disease. It and tonsillectomy give us some hope for the future. In some other diseases such as pneumonia and meningitis, which once in a while attack the heart, we have to a certain extent specific antisera which would tend, by shortening the course of the disease, to prevent heart involvement.

Second in importance in the treatment and prevention of cardiac involvement in acute infectious disease is good nursing care. During the war, when often we were short of medical officers and very low in drugs, we found we got along surprisingly well if only we had good nurses. So in infectious disease, with or without heart involvement, the patient should be carefully nursed.

Finally, we have symptomatic drug therapy. Here is where the difficulty comes. Much of this treatment is empirical and there is great need for accurate and painstaking observation. I feel that much time and money have been wasted in giving all manner of "stimulating" drugs to patients with circulatory or general failure in infectious disease. Once in a while a patient seems to be tided over a crisis by this therapy, but nineteen others fail to respond. We are liable to feel, in our present state of knowledge, because of an occasional apparent successful response, that we should stick to it and fill every one with drugs. While working in a typhus epidemic in Eastern Macedonia two years ago a colleague of ours got typhus fever. The Greek military surgeons urged that they be allowed to treat him with frequent subcutaneous injections—caffeine, camphor, adrenalin and strychnine. We objected and they warned us that he might die if he did not receive these drugs. We got two excellent American nurses, gave him no drugs and he had an early crisis, on the tenth or eleventh day, without complications. Of course such a case is of little moment except to show the present chaotic situation in regard to such therapy. We must get more light on these points so that our treatment will be more reasonable. One well-trained man gives digitalis as a routine to all patients with pneu-

monia, another decries it and gives none except as heart failure may be manifested. Which is right? This is an important question, for if we can prove that digitalis always helps in pneumonia we should always give it. On the other hand if it rarely helps and perhaps often makes more toxic, for it must be remembered that digitalis is a poison, when should we give it, if at all? Cohn and Jamieson<sup>4</sup> have shown that digitalis has an undoubted influence on a fever heart, but are we sure that this influence is a good one? T. Stuart Hart<sup>5</sup> has reported a study of digitalis action in bronchopneumonia, and he states that there was absolutely no difference in the course of the disease or the pulse-rate between the digitalized and the non-digitalized cases of bronchopneumonia, except in two cases of chronic cardiovascular disease with auricular fibrillation, which were much benefited. Extensive experiments of this sort are necessary not only with digitalis but with other drugs, such as caffeine and camphor. Once upon a time, not so very long ago, strychnine and alcohol were prescribed very freely at the Massachusetts General Hospital in pneumonia and other infectious diseases. The medical generation coming along now in Boston has hardly heard of such therapy except as of historical interest. This may be wrong, but I do not believe it is. We are a people of fads and fancies, and it seems to me that just at present the fad is digitalis, as a routine to avert circulatory failure in infectious disease. I want to urge further study of this important question.

**Summary.** In conclusion, then, it may be said that the heart is affected in two ways in acute infectious disease: First by direct permanent damage to endocardium, myocardium, and pericardium, and second by temporary poisoning. For both of these conditions it is necessary, first, to combat the infection itself by specific therapy, if there is such, and by good nursing care. The symptomatic therapy of cardiovascular symptoms and signs in the prevention of failure is on a very uncertain basis at present and needs further investigation. The routine employment of digitalis in such infectious diseases as typhoid fever and pneumonia is unwarranted. Finally, the frequent occurrence of the effort syndrome during and following infectious disease and simulating at times cardiac disease is in need of emphasis.

<sup>4</sup> Jour. Exper. Med., 1917, 25.

<sup>5</sup> AM. JOUR. MED. SC., 1919, 168; Jour. Am. Med. Assn., 1919, 78.

## THE DIAGNOSIS OF TUMORS OF THE CAUDA EQUINA, CONUS AND EPICONUS MEDULLARIS: A REPORT OF NINE CASES.

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TUMORS of the cauda equina and conus medullaris are not rare, and there has been no dearth of literature on the subject. Spiller, in 1908, reviewed all the literature up to that year and described eight cases that he had seen. Since then many other excellent articles have been published and new cases added to the number already recorded. It is therefore with some hesitancy that I venture to add to this long list my own observations on a few cases examined at the Mayo Clinic with a short account of each. Only cases in which the presence and location of a tumor had been definitely established by operation are recorded here, together with another case which is of interest from the point of view of diagnosis.

I have found eight cases of this disease in the records of the Mayo Clinic, since 1916, and five of these I had the privilege of observing during my service in the Section on Neurology.

The eight cases were selected from thirty-three cases of spinal cord tumors that were observed from January 1, 1916, to January 1, 1921—a somewhat high rate of incidence when it is considered that Steinke, in 1918, found only thirty cases of tumors of the cauda equina and lowest segments of the spinal cord in an analysis of 330 cord tumors.

### REPORT OF CASES.

CASE 1 (248240). Mrs. C. L. B., aged twenty-nine years, came to the Clinic October 11, 1918. She complained of pain in the back and a limp in the right leg. Since the birth of her baby, two years before, she had had pain around the area of the first and second lumbar vertebra, which had gradually grown worse in spite of various treatments. In July, 1918, she noticed that her right foot was becoming weaker and that it was difficult to stand on the ball of that foot. This also had become progressively worse, so that she had to raise her foot to clear the ground. The function of her bladder was normal and she was not conscious of any loss of sensation. The pain radiated down the back of the right leg, and in getting out of bed in the morning she had a tingling in the soles of her feet. She felt better sitting and had to leave her bed for four hours at a time to sit in a chair.

Examination revealed almost complete loss of power in the calf of the right leg and the peroneal and anterior tibial muscles of the right foot. There was a hypotonus of these muscles and fibrillary twitchings were seen in the peroneal and anterior tibial muscles.

Both patellar reflexes were exaggerated, but no definite Babinski sign was seen. The Achilles reflex on the right was absent; on the left it was diminished. Both external hamstring tendon reflexes were absent. The patient's gait was steppage in type and there was a very slight diminution of sensation to pain and temperature over the posterior surface of the right thigh (Fig. 1). Touch sensation was normal. Pressure on the eleventh and twelfth dorsal spines, which were prominent caused definite severe pains to radiate down

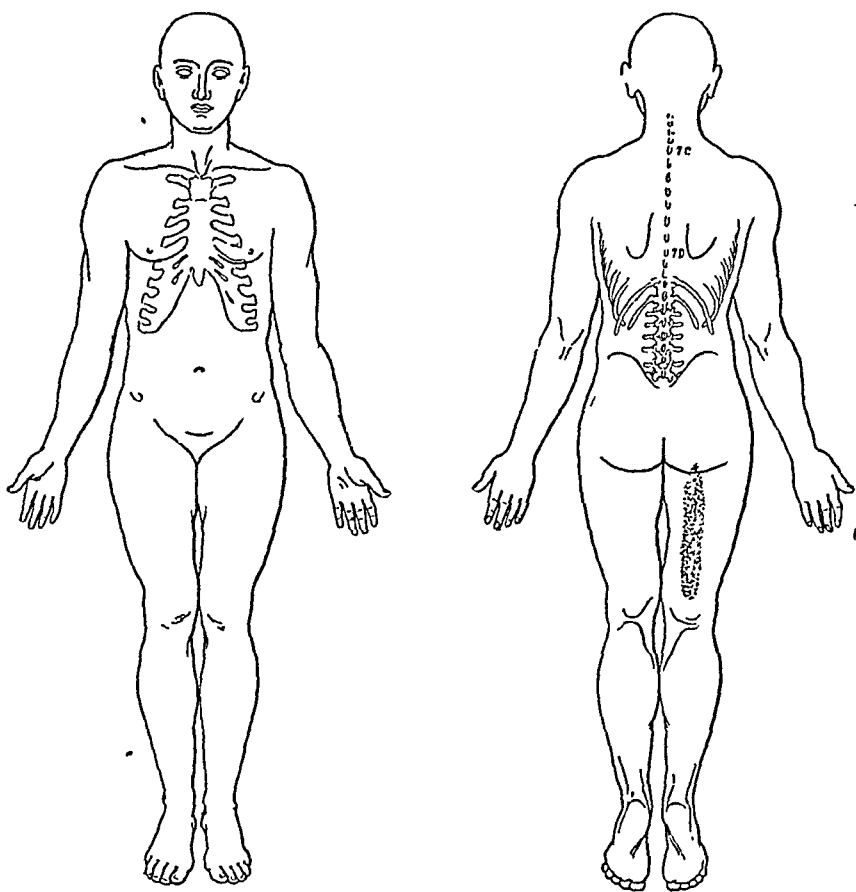


FIG. 1.—Case 1 (248240). No incontinence of urine or feces. Intradural extra-medullary, encapsulated glioma. (Complete ■■■■, partial ■■■■, slight ■■■■ loss of sensation of touch, temperature, and pain).

the posterior aspect of each thigh. Pressure on the sacrum did not cause pain. Roentgenograms of the lumbar spine revealed nothing abnormal, but the spinal puncture produced a yellow fluid which became almost solidified when the Nonne test was performed. A small spontaneous clot and a heavy coagulation formed with boiling. A diagnosis of an intradural extramedullary tumor of the cauda equina was made. A laminectomy was performed October 30, 1918 (Dr. Adson), and a reddish-gray encapsulated intradural extramedullary tumor was seen extending from the eleventh dorsal verte-

bra to the upper border of the fourth lumbar vertebra. The tumor, a glioma, was 15 cm. long and 1.5 cm. in diameter.

CASE 2 (279754). A. B., a boy, aged sixteen years, came to the Clinic, August 14, 1919. He complained of pain in the right lumbar region. Twelve months before he had noticed an intermittent dull pain in the right lower quadrant of the abdomen and right lumbar region. This lasted from two to three days and was then absent

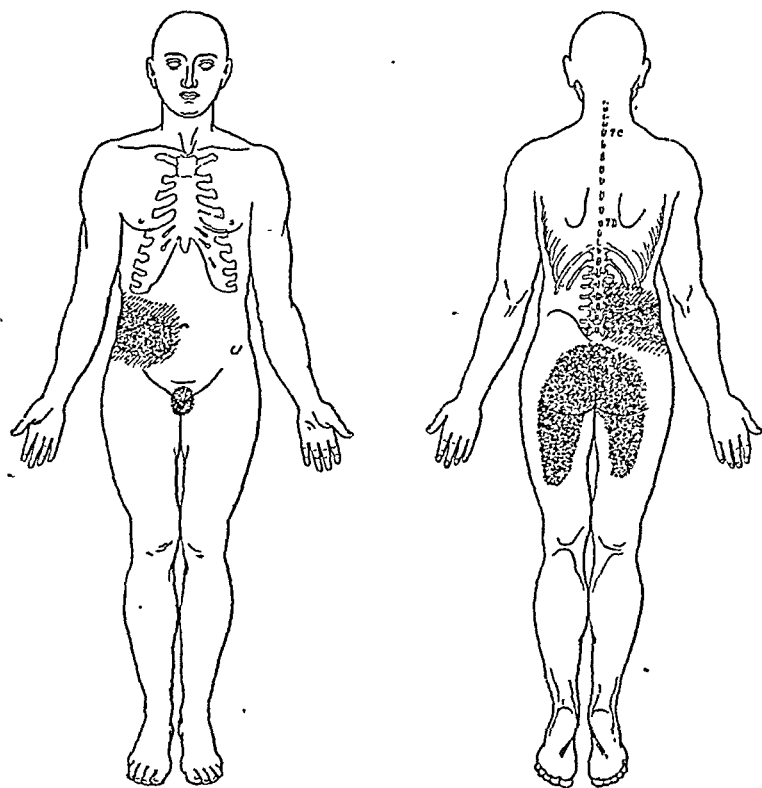


FIG. 2.—Case 2 (279754). Incontinence of urine and feces. Extradural secondary carcinoma. (Hyperesthesia to touch, temperature and pain [shaded]).

for one week. At times the pain passed over both hips, sacrum, and down the back of both legs. He described it as a "numb" pain, with a feeling of pin and needle pricks in the skin covering the right lower quadrant of the abdomen. Six months before he had had his appendix removed for this pain, without relief. He had difficulty in holding urine at times, but no trouble in starting.

The patient returned to the Clinic December 22, 1919. The pains were worse and still in the right lower quadrant of the abdomen, the back, and the posterior aspect of the thighs. He felt a girdling

sensation over the lower thorax. About twelve months from the onset of pain he began to lose power in his legs and was forced to use crutches. Six weeks before his second visit to the Clinic he became unable to walk at all. Fourteen months from the onset he had to use a catheter to empty his bladder and had no control over bowel movements. He had pain in the legs when he coughed or even swallowed.

Examination of the patient showed an atrophic atonic paresis of both lower extremities equally distributed in all muscles below the glutei and the psoas. He had an anesthesia over the area supplied by all spinal cord segments below the first sacral, and a large patch of greatly diminished sensibility on the right side occupying the right lower quadrant of the abdomen in front and the area of skin included between the second lumbar spine and the fifth lumbar spine behind (Fig. 2). The margins of this area were hyperesthetic, especially over the eleventh dorsal to the first lumbar spinous process. He could neither stand nor walk and he was incontinent of both urine and feces. Patellar, Achilles, and plantar reflexes were absent and the feet were very much swollen. The spinal puncture disclosed a milky, cloudy fluid containing seven small lymphocytes for each cubic millimeter; it clotted readily. The Wassermann reaction was negative, but the Nonne test was positive. A diagnosis of cauda equina tumor was made.

The patient was operated on, December 30, 1919, by Dr. Adson who found an unencapsulated cellular mass, extradurally situated opposite the eleventh and twelfth dorsal and first, second, and third lumbar vertebræ, with a small projection running laterally and anteriorly to the cord as high as the ninth dorsal vertebra, also extradural. The tumor involved both the bone and dura extensively and was reported to be a secondary carcinoma, although no primary source was discovered.

CASE 3 (294401). Mr. F. E. M., a thin poorly nourished man, aged forty-two years, came to the Clinic October 24, 1919, complaining of pain and weakness in both legs. Five months before there had been a gradual onset of pain and numbness in the left lower extremity along the posterior aspect of the left buttock, thigh, and leg. This pain had persisted and increased in severity. Two months before pain and numbness began in the right leg. Weakness in the legs and difficulty in walking appeared about two months before, and he had noticed that the muscles of the thighs and calves had become smaller. He had to use crutches and felt that he was getting rapidly worse. The stream of urine was often interrupted and had but little force. He had a sensation of swelling in the rectum and recently had become constipated.

At examination the left lower extremity was weak, but not actually paralyzed. The power of the right leg was only slightly diminished.

The muscles were atonic and atrophic, but no fibrillary twitchings were seen. Both tendo Achillis reflexes were absent and the patellar reflexes were almost absent. Sensation was not greatly disturbed, although there was some loss of sensation to pain and touch along the posterior aspect of the thigh, buttock, and leg in the area supplied by the fifth lumbar to the fifth sacral segments of the spinal cord of the left side. Control of the bladder and rectum was greatly diminished and a Kernig's sign was present on the left side. The left sciatic nerve was tender. A spinal puncture was performed October 18, 1919, and while the Wassermann and Nonne reactions were negative, there were a great number of pus cells in the fluid. A tentative diagnosis of localized subdural abscess was made and laminectomy was advised.

Operation was performed, October 30, 1919 (Dr. Adson). After the laminectomy an extradural malignant glioma was seen in the spinal canal; it extended from the third lumbar vertebra to the end of the sacral canal. Some of it extended anteriorly and on several of the caudal roots, forming separate tumors as they left the dura. An inflammatory band was stretched across the dura compressing it so that a small cyst was formed. This contained cloudy spinal fluid and communicated with the subdural space.

CASE 4 (310356). Mr. O. G., a poorly nourished man, aged thirty-two years, was brought in a wheel chair to the Clinic, March 27, 1920. He complained of pain in his back and of not being able to walk. Eight years before, while wrestling, he hurt his back and at different intervals since then he had had pain in the middle lumbar region. In March, 1919, he had noticed difficulty in starting urine, and about August he felt tingling in the soles of his feet and his lower limbs began to become weak and difficult to control. He used a cane from August to January, when he was forced to use crutches, and even this was difficult. In September, 1919, the pain became very much worse and spread to the legs, abdomen, and hips. He described it as a "pulling, sharp" pain growing steadily worse. In January, 1920, he found he had to use a catheter to empty the bladder. He was constipated, but feces did not leak when they were liquid. He had frequent erections, four or five each day, but he could not ejaculate. The pain and numbness extending from the epigastrium to the legs was especially bad when he was lying down, and he had to sit up to sleep for the past two or three years, using three or four pillows under his back.

Examination showed an almost complete atrophic loss of power from glutei downward with fibrillary twitchings on the left side. Patellar and Achilles reflexes were absent and there was no Babinski sign. The abdominal, hypogastric, and cremasteric reflexes were absent, but the epigastric reflex was present. He could neither stand nor walk and his lumbar spine was held rigid. There was no

particular tenderness except from a recent spinal puncture. His feet and legs were anesthetic to pain, touch, and temperature, and his thighs were partially so. The level between disturbed sensation and normal skin was not clear-cut, but was within the area supplied by the third lumbar segment, so that sensation was normal above that segment, but descended from only partial loss at that segment to complete loss around the second, third, fourth, and fifth sacral segments. Spinal puncture was attempted but resulted in a "dry tap." The roentgenograms revealed nothing of note in the bones and the sacrum. The Wassermann reaction was negative. A diagnosis of a cord tumor involving the cauda equina was made.

At operation, April 7, 1920, (Dr. Adson) a large, elongated, soft, well encapsulated, intradural, endothelioma was found, extending from the tenth dorsal vertebra to the fifth lumbar vertebra; thus it was about 20 cm. long, situated on the dorsal aspect of the cauda equina and extending above the conus terminalis.

CASE 5 (315328). Mr. W. H. P., a pale, undernourished man, aged fifty-two years, walking with the help of a cane, came to the Clinic May 10, 1920, stating that he had locomotor ataxia. He complained of pains and numbness in his legs and difficulty in walking.

Three years before he had experienced a painful, burning numbness in the left foot which lasted about one hour. Four or six weeks later the same feeling returned in the same place and for the same period of time. Gradually these sensations became more frequent and lasted longer. Two years before, the same sensation commenced in the right foot and leg and for one year both were about equal, but for the last year the pain had been more severe in the right leg. A year before his sexual power began to fail, and when he came to the Clinic was almost absent, but the functions of the bladder and rectum remained normal. About twelve months before he began to lose power in his lower extremities and had to use a cane; this grew progressively worse. In the left leg the pain was more of a burning numbness, but in the right leg it was cramp-like and, as he described it, it "grips me like a bull-dog." He had difficulty in controlling his gait and was afraid to venture out after dark. His pain was relieved by walking and movement and was made worse by lying down.

Examination revealed that the patient had a weakness in his lower limbs, most severe in the hamstring, peronei, anterior tibial, and toe muscles, or the muscles supplied from the fourth lumbar to the first sacral segment in the spinal cord. The muscles supplied by the second sacral or third lumbar segments were much less affected. Sensation to touch, temperature, and pain was equally and severely disturbed over an area supplied by the fourth lumbar, fifth lumbar, and second sacral segments of the cord (Fig. 3). The sensation of skin areas corresponding to one segment below and one above



these segments were markedly less interfered with. The line of demarcation between normal and abnormal sensation was not clear-cut and the sensory disturbance around the anus was almost negligible. The anterior surface of the thigh was normal. Both motor and sensory disturbance corresponded to the segmental area supplied by the fourth and fifth lumbar, first sacral and part of the second sacral segments. Pressure sensibility was normal, but both vibration and joint sensibility in both lower limbs were severely dimin-

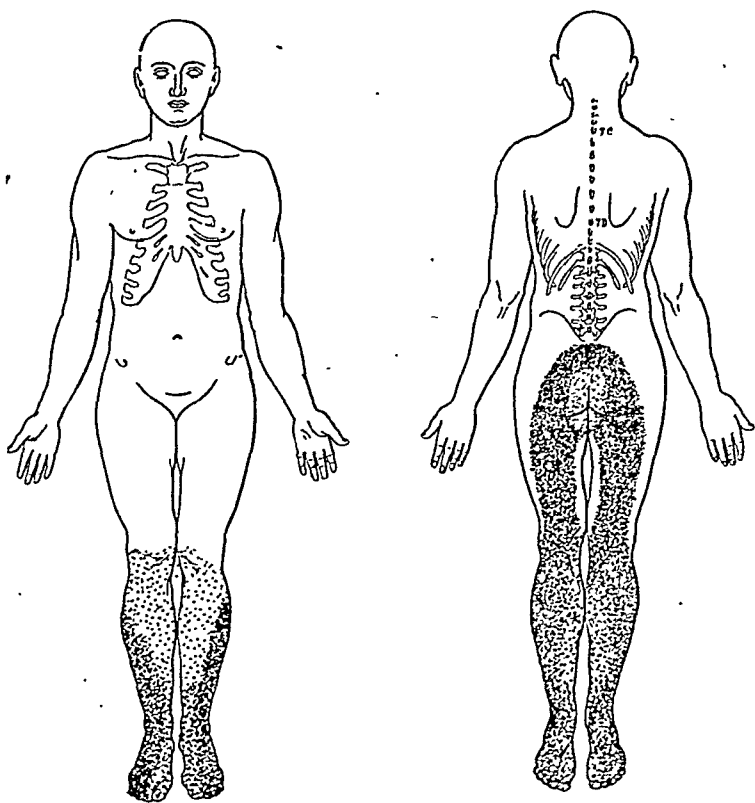


FIG. 3.—Case 5 (315328). No incontinence of urine or feces. Intramedullary epiconus tumor.

ished. The patient's gait was very ataxic. There was no dissociation of sensation. The patellar reflexes were diminished and the Achilles and cremasteric reflexes were absent. There was no Babinski sign. The weakened muscles were both atrophic and atonic and showed abundant fibrillary twitchings. Distinct pain was felt on squeezing the Achilles tendon, adne xcept for the segmental areas mentioned, there were no disturbances of sensation anywhere on the body. The spinal fluid examination showed a positive Nonne

reaction, a negative Wassermann reaction and five lymphocytes. A diagnosis of cauda equina tumor was made.

Operation was performed, June 1, 1920 (Dr. Adson) and an intramedullary tumor bulging the lower portion of the cord above the cauda equina was found. The cord substance was infiltrated and a second operation was deemed advisable. Unfortunately the patient died before this could be done.

CASE 6 (315631). Mrs. R. J. F., a thin emaciated woman, aged twenty-eight years, was brought to the Clinic in a wheel chair, May 12, 1920. She complained of being unable to walk and of having pain in her legs. She had had an appendectomy and bilateral partial oöphorectomy performed for her trouble without relief. Two and one-half years before she noticed a sore, burning spot localized to the right great trochanter. This lasted three months and then finally disappeared. Two years before she had sudden severe pain in the hips and the lower lumbar region, worse at night, and about the same time she noticed slight weakness in the lower limbs. This attack of pain lasted about two months. Twelve months before she had to have assistance to walk, and for the last two months had not been able to walk at all. The left leg was worse than the right. As weakness increased, pain diminished in severity until little or none remained. She had not had incontinence of urine, but the flow was hard to start at times. She complained of being constipated and of the stools escaping when liquid. The pain occurred at night, causing her to sleep sitting up. Walking seemed to relieve the pain, which was most intense over the right great trochanter. It never had radiated down the back of the thighs.

At the time of examination the patient was unable to walk, owing to an atonic atrophic paralysis of the peronei, anterior tibial, and the toe muscles. Her calves, thighs, rotators, and adductor muscles were less affected, also the psoas and quadriceps. Weakness in each leg was about equal and the muscles supplied by the spinal segments below the fourth lumbar were most affected. Those supplied by the second and third lumbar were less so. She had an almost complete loss of sensation to touch, temperature and pain over the skin areas supplied by the fourth and fifth lumbar and the first sacral segments, and a small amount of sensation remaining over the left instep. The skin areas of the second, third, fourth, and fifth sacral segments, though hypæsthetic, seemed to be much less affected. There was a patch of hyperæsthesia over the right posterior inferior iliac spine. Patellar, Achilles, and plantar reflexes were absent, and over the legs there was a loss of pressure sensation. Both joint and vibratory sensibility were seriously damaged. There was a permanent shortening of both hamstring groups of muscles, due apparently to the patient having remained sitting up night and day for a long time. The greatest damage was shown in areas

supplied by the fourth and fifth lumbar and first and second sacral segments of the spinal cord. A spinal puncture resulted in a "dry tap." A diagnosis of tumor of the cauda equina was made.

Laminectomy was performed, May 25, 1920 (Dr. Adson). An ependymal cell glioma, 3 cm. in diameter, extending from the eleventh dorsal vertebra above to the fifth lumbar vertebra below, was found. It had infiltrated both the cord and the roots of the cauda equina and extended into the sacral canal.

CASE 7 (341502). Mrs. J. S. G., aged twenty-five years, came to the Clinic, November 20, 1920, complaining of pain in her right hip. Two and one-half years before she had felt the pain over the tuberosity of the ischium on the right side and over the outer surface of the right leg. The pain came on during her third confinement and lasted until the birth of a healthy child. It reappeared three weeks afterward and lasted for four months. She had no symptoms during the winter of 1918, but in February, 1919, pain commenced again in the same two places and was more severe, lasting this time about four months. During the winter of 1919 and 1920 she was free from pain, but in March, 1920, it started again and persisted. In July her feet became swollen and she found that her back was stiff and a sudden jar to the spinal column caused the pain to radiate along both sciatic nerves. Gradually increasing pain in the lumbar spine was noted. In October, 1920, she discovered that she was not voiding urine for considerable periods, and then a large quantity would pass involuntarily. The urine had a strong odor. Feces escaped when liquid, and gas was not retained. She had not noticed loss of sensation, and she was sure that her limbs had complete power and that she could walk and run as well as ever. She described her pain as dull, burning, and constant, felt in the lumbar spine, tuberosity of the ischium and outer side of the right leg. It kept her awake at night and she found some relief in sleeping sitting up. In all her spells of pain she had slept sitting in a chair, and at times had had greatest relief by sleeping with her knees on a chair and her trunk on a table face down.

Examination revealed a well-developed woman, with loss of muscular power, and walking without even a limp. There was a loss of sensation to pain, touch, and temperature over the area supplied by the second, third, fourth, and fifth sacral segments on the right side and the fourth and fifth segments on the left side. There was also a partial loss of sensation over the fifth lumbar and first sacral segment on the right side (Fig. 4). Patellar and Achilles reflexes were absent, and there was no Babinski sign on either foot. Kernig's sign was present on the right side and there was marked limitation of movement of the lower part of the spine. She had pain in the lumbar spine when lying on her back and local tenderness over all the lumbar spines. Pressure over the third, fourth, and fifth lumbar

spines produced pain radiating down the sciatic nerves. The sphincter control of the bladder and the rectum was partially lost and both anal and hypogastric reflexes were absent. The roentgen examination of the lumbar and sacral vertebræ showed nothing of note. The spinal fluid Wassermann reaction was negative. The Nonne test was positive. A diagnosis of cauda equina tumor was made. An exploration was made of the cauda equina November 30, 1920. (Dr. Adson.) A large ependymal cell glioma was found, the

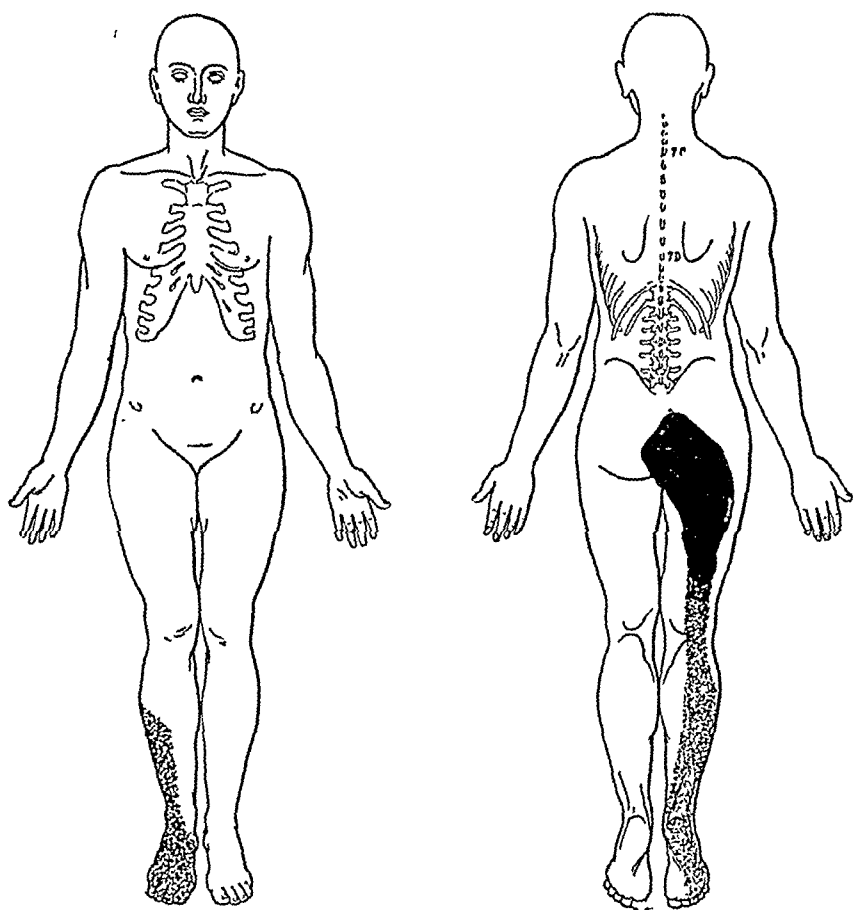


FIG. 4.—Case 7 (341502). Incontinence of urine and feces. Ependymal cell glioma involving the cauda equina.

upper level of which was as high as the second lumbar vertebra, while its lower part has invaded the dura, bone, and even the lumbar muscles at the lumbosacral juncture, and it filled the sacral canal below. Its upper portion was intradural and extramedullary, but the lower portion had infiltrated the lumbar muscles to within half an inch of the skin.

CASE 8. (341775). Mr. A. C. H., a poorly nourished man, aged twenty-seven years, came to the Clinic, November, 1920, complaining

of pain in the lower part of his back and the back of his legs. Five years before he had had an attack of severe pain along the course of both sciatic nerves. This lasted two weeks. Another similar attack came on four years before, lasting one week. About this time he noticed that a blow in the back caused pain to shoot down his legs. About two and one-half years before his back became stiff and motion or jarring of his spine produced severe pain. He was then in France driving an autotruck, which jarred him so much that

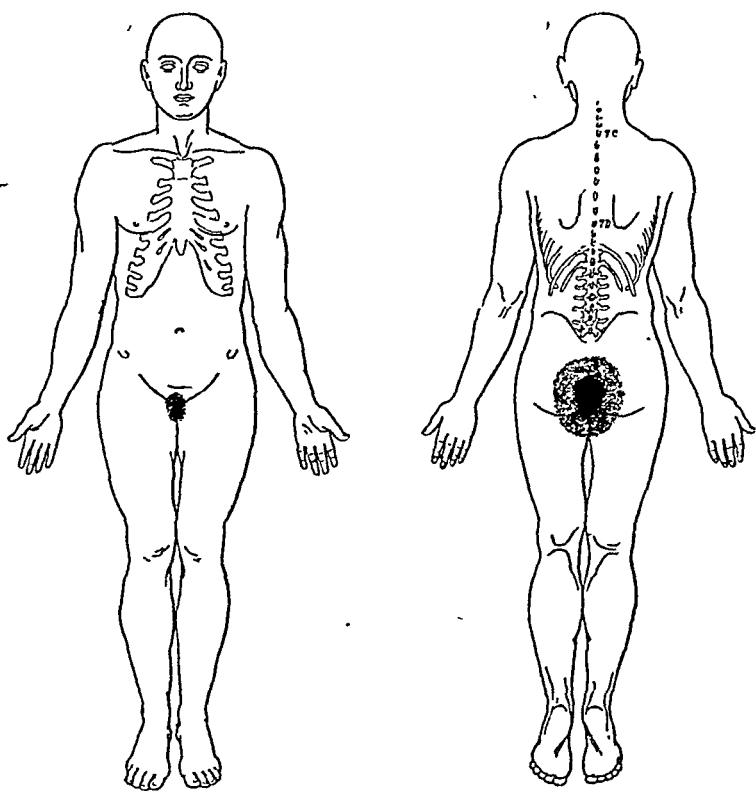


FIG. 5.—Case 8 (341775). Incontinence of urine and feces. Ependymal cell glioma involving the cauda equina.

he had to cease work and was invalided home. On the journey home he had painful spasms of the hamstrings and calf muscles, so that his legs were doubled under him at times. Two years before he found that he had difficulty in expelling urine, and this trouble became gradually worse, so that in the last six months he had to use a catheter. He had difficulty in retaining liquid feces and gas. The pain was a dull ache, like toothache, felt most in the lower lumbar spine and posterior aspect of each thigh. It hurt him to sit on a

hard chair. He felt better in the morning. Movement and walking brought on the pain and he felt better if he remained quiet.

At examination a well-marked weakness of the lower limbs, although not of great degree, and a rigid painful lumbar spine were found. The patient walked slowly and painfully but with a definite limp. The muscles were atonic and atrophic, but there were no fibrillary twitchings. The patellar and tendo Achillis reflexes were almost absent. The anal and bulbocavernosus reflexes were absent and the cremasteric reflex was almost absent. There was a well-marked anesthesia over the skin supplied by the fifth sacral segment on each side, and the third and fourth sacral segments seemed also a little disturbed, so that, on the whole, sensory changes were slight (Fig. 5). Over the fourth lumbar spine there was a spot of exquisite tenderness; pressure there produced pain that radiated down both legs. Sensation of vibration was diminished in both lower extremities. Both sciatic nerves were tender and Lasegue's sign was present. Roentgenograms revealed a round symmetrically placed area of diminished density at the level of the first and second sacral vertebrae. It was impossible to estimate its significance previous to operation. Spinal puncture, although repeated once or twice, was not productive of fluid. A diagnosis of cauda equina tumor was made.

Operation was performed, December 7, 1920 (Dr. Adson), and an ependymal cell glioma was found, extending from the eleventh dorsal vertebra to the second sacral vertebra, with obvious further extension upward. It was also found that the laminae of the first, second and third sacral vertebrae were missing, constituting a spina bifida. In this space was some yellow fluid and the tumor extended into it.

### GENERAL CONSIDERATIONS.

In studying the course, symptoms, and signs of this disease, there is always before us the desire to discover some common factors which might make its recognition easier in the future. If this disease followed a course of mathematical exactitude all would be well, but also there would be no need of a diagnostician. In the vagaries and eccentricities of the disease we have ample scope for training ourselves in the diagnosis and localization of spinal cord tumors. Tumors in this portion of the vertebral canal present a completely different picture from that shown by tumors higher up, and, further, tumors at widely separated levels may give almost identical signs and symptoms.

The combination of sphincter disturbance, atrophic paresis of the lower limbs and perianal anesthesia is characteristic of the disease, but the determination of the position and extent of the tumor mass is in some cases an impossibility. Reference to Case 9 will demonstrate this fact.

All of these cases are different and each is worth a close study. To draw any but general conclusions from them when studied in the aggregate would be to invite error, and perhaps the most obvious fact observed is that the more closely they are studied the more they seem to differ.

**PATHOLOGY.** The strongest factor in the production of differences in course, symptomatology, and physical signs is the nature of the tumor in each case. The more malignant the type of tumor the more rapid will be the course and the more diffuse the signs, while a slowly growing tumor will have a long course and clear-cut signs. It is well to contrast the picture shown in Case 3 with that shown in Case 4. In the former there is a short history and a diffuse distribution of signs and symptoms; in the latter the history is long and the signs are clear-cut, distinct, and symmetrical. The cases of giant endotheliomas of the cauda equina described by Collins and Elsberg had a relatively long course, but the tumors were not encapsulated and spread in all directions, filling the sacral canal. Here also the signs were few, patchy, irregular and affected different roots and segmental areas with varying degrees of intensity. Since a relatively malignant tumor may spread in any direction from its origin and may spread upward or downward, intradural or extradural, an arbitrary classification of such tumors on the basis of their position is completely useless, for a tumor that one would expect to find clearly intradural and confined to a small area on operation might be found to have a wide and destructive situation.

The sacral canal, as compared to the other portions of the vertebral canal, is relatively wide and a tumor may grow for a long period without giving any localizing signs. A tumor in the dorsal canal as soon as it infringes on the posterior nerve roots or any part of the cord will give a sharply marked level (unless it be intramedullary), but a tumor in the sacral canal, where the first sacral root is as long as 14 cm., does not announce its position with such a degree of exactitude.

Of the eight tumors only two were encapsulated, and one was diagnosed by the pathologist as an endothelioma and the other a glioma. The remaining six cases, with the exception of Case 5, were tumors which showed a tendency to erode the dura, bone, and muscle approaching even to one inch of the skin (Case 7). Case 5 was obviously a relatively benign tumor, but no pathological diagnosis was made.

CASES 6, 7, and 8 were ependymal cell gliomas and the course of the disease, as well as the findings at operation, were somewhat similar. In these patients the tumor filled the sacral canal and extended up into the lumbar region higher than the surgeon thought it safe to invade. These tumors have a long insidious course and produce a great amount of destruction of everything they encounter with surprisingly few signs. Case 7 is a good example of the course

and signs of such tumors. Clinically in their degree of malignancy, such tumors come midway between so-called malignant gliomas and encapsulated gliomas. They are destructive in their progress but are relatively slow growing. The more salient features of the symptomatology of these eight cases were as follows:

**PAIN.** The earliest and most constant symptom in this disease is pain. It is also the most distressing feature. It may appear many months, even years (Cases 4 and 8), before any sign of the disease is established, and, whereas at first it is light and intermittent, with long intervals of freedom, later it becomes constant day and night and leads the patient to adopt any means to obtain relief. In a few of the patients a solitary attack of pain appeared months before it was repeated; why there should be so long an interval is difficult to explain.

The patients soon discovered that movement relieved them of their agony, and, while jarring and sudden movements initiated a spasm of suffering, on the whole their pain was less severe while they were walking. Five of the 8 patients had slept sitting up in a chair for months, and when they were no longer able to walk, remained day and night in the chairs in which they were wheeled. One patient (Case 6) had a permanent contraction of her hamstrings from such a position. In five patients there was an intolerance to the prone position in bed. One patient (Case 8) spent nights kneeling on a chair and lying face downward across the table. This attitude was noted also by Schmoll in a case he recorded. The pain was either diffuse and radiated from the back down the posterior aspect of the thighs, so that the patient moved his hand over a large area in pointing to the site of his pain or he pointed to one isolated area as being the site. This was noted in Cases 5, 6 and 7.

The tumor in Case 5 was intramedullary and in Case 6 it was probably so placed at the commencement of the disease. Both of these patients pointed to one spot as being the constant position of the pain; there was no radiation along the sciatic nerves.

Pain in the lumbar spine was not confined to cases in which the vertebræ were actually eroded. It seems to have been felt even in Case 5 in which the tumor was definitely intramedullary. The pain was also severe in this case, but certainly not so severe nor so well marked as in the cases in which the vertebræ were actually eroded and the spinal column was rigid. Such lumbar pain is valuable at times for localization, as may be noted in Case 1, in which the pain and tenderness were over the exact site of the tumor. Some pain was felt as a result of root irritation, but it was felt some distance away. That is, the pain in the back was over the posterior aspect of the right thigh. Pain in the back, therefore, is not confined to cases of tumors eroding the vertebræ; it is common in caudal tumors and even in purely intramedullary conus tumors.



To find where the pain was first felt is valuable as an idea of the starting-point of the tumor, and by comparing it with the widest limit of the pain in the later stages of the disease a good idea of the spread of the tumor may be gained.

The nature of the pain is important as a point of differential diagnosis from such diseases as tabes dorsalis and multiple neuritis. The patient in Case 5 described his pain as cramp-like or a burning numbness. Quite different from the flash-like pain of tabes from which he was supposed to be suffering. In two cases the pain was suggestive of motor irritation as well as sensory, as there were painful cramps of the muscles (Cases 5 and 8). Many of the patients described their pain as a steady, constant, burning *aché*.

**TENDERNESS OF THE SPINE.** Tenderness of the back was present in Cases 1, 7, and 8, and was of extreme diagnostic and localizing value in Case 1. In this case pressure on the eleventh and twelfth dorsal spines produced severe pain, radiating down the posterior aspect of the thighs; pressure on the sacrum produced no such result. This was almost certain information that the tumor lay under this tender area. Tenderness was also well marked in Cases 7 and 8, but it is well to note that while in Case 1 there was a benign encapsulated tumor the other two tumors had eroded bone and muscle in all directions. Tenderness, while suggestive of vertebral involvement, is not conclusive. In Case 4 tenderness was absent though sought for. A careful palpation of the lumbar spine should never be neglected in cases of suspected tumors. Rigidity of the lumbar spine was associated with marked tenderness in Cases 7 and 8.

**MUSCULAR WEAKNESS.** Seven of the eight patients were weak in their lower extremities; it was the most prominent symptom in Case 1. The degree of weakness varied; it was slight in Case 3, and there was complete loss of power to stand or walk in Cases 4 and 6. In spite of a long history of severe pain and definite sphincteric and sensory disturbances weakness was absent in Case 7. It was not the earliest symptom nor was it an isolated finding in any of the cases. It was associated with sensory and sphincteric disturbances in all the cases. Paresis of the lower limbs without other physical signs, and even with some pain, does not establish the diagnosis of tumor in this region. For this reason it was difficult to make a diagnosis in Case 1, in which there was only a mild sensory change, without sphincter disturbances. Other factors such as the condition of the spinal fluid, and pressure tenderness helped in making the diagnosis. The muscular weakness was neatly selective in Case 5, in which an intramedullary tumor was confined to a few segments in the epiconus; in the other cases the weakness was diffuse and useless for localization. In only one case (Case 1) was weakness unilateral; in Case 3 it was asymmetric. In the remaining 5 cases in which weakness was present it was equally distributed over the

two extremities, especially in Cases 2, 4 and 6, in which the weakness was severe and the disease well advanced.

**SPHINCTERIC DISTURBANCES.** Five of the eight patients had difficulty in controlling the bladder. Next to pain it was the earliest symptom in three. It was not an isolated phenomenon, as in each case it was associated with a perianal or saddle hyperesthesia or anesthesia. In three instances catheterization was necessary to empty the bladder. Rectal control seemed to have been affected in proportion. In one case (Case 5) there was loss of sexual power without loss of control of the bladder or rectum. In Case 4 the ejaculatory part of the sexual act was abolished; the power of erection was maintained. This corresponds to the case of pelvic tumor recorded by Müller and discussed by Spiller, who regarded this phenomenon as being an indication that the fibers for erection leave the cord at a higher level than those supplying the bladder, rectum, and ejaculatory muscles. In Raymond's table the center for ejaculation is said to be in the third sacral segment and that for erection to be in the second sacral segment. These two points are close in the conus. Sanders found a patient who also had genital anesthesia and incontinence of urine with preservation of the function of erection. He interpreted this as being proof that the tumor could not be in the conus on account of one of two centers so close together having been spared. In Case 4, while the tumor did not infiltrate the conus it certainly pressed on it, and I believe with Spiller that it is more satisfactory to explain this phenomenon by regarding the erection center as being at a somewhat higher level than the ejaculatory center and the fibers supplying it to leave at this higher level. Further, it is possible that the center is in the sympathetic ganglia outside the cord altogether. This would explain its escape in lesions of the conus and its freedom from impairment of function. A case such as Sanders recorded does not, in my opinion indicate that the conus was undamaged. Three patients either did not have paralysis of the bladder or it was but little disturbed. In these cases (1, 5 and 6) there was a diversity of pathology. The first patient had a well-encapsulated tumor, the second an intramedullary epiconus tumor above the third, fourth, and fifth sacral segments, and in the third patient the conus and cauda were extensively involved by a malignant tumor, and why he should have been free from severe bladder and rectal incontinence is a mystery. At the same time the sensory disturbance in the third, fourth, and fifth sacral segments was not well marked, indicating possibly a relatively slight degree of involvement of the segments and their roots. Frazier reports a similar case, but without the degree of involvement that was shown at operation or even before operation in this case (Case 6).

These three patients were ill two years, two and one-half years and three years respectively, and yet no bladder disturbance was manifest in that time. Spiller reported two cases, one of two years'

and the other of seventeen months' duration, before death or operation. Neither of these patients had sphincteric disturbance.

Lack of control of the bladder and rectum is therefore not always present in cases of caudal and conus tumors even though the other changes, not excluding even sensory changes, may be severe. The three patients in this series might possibly have developed incontinence had they been allowed to continue, yet they had ample time to develop it prior to operation.

**SENSORY CHANGES.** All the patients had some degree of sensory loss, but the degree varied from a slight loss of sensation, of which the patient was ignorant (Case 7), to complete anesthesia of the lower extremities (Case 4).

The history of sensory change has less value than the other subjective complaints. In three cases any hypesthesia was denied and a patient's statement that there is no sensory change should not be relied on. Some complained of numbness, a cold sensation, and tingling. In three cases only was there any symmetry of distribution of the anesthesia. In one of these the anesthesia was in the fifth segmental skin area, in the other two over the buttocks and back of the lower extremities with involvement of the anterior surface of the leg, but not the thigh. The anesthesia in Case 5 gave more than a hint of the localization of the tumor in the epiconus (fourth and fifth lumbar and first and second sacral segments).

The patch of anesthesia found in the right lower quadrant of the abdomen in Case 2 was shown at operation to have a definite pathologic basis in the branch of the tumor growing up the spinal canal. The slight degree of severity of the sensory changes in the third, fourth, and fifth segmental skin areas in Case 6 was shown to correspond with the position of the tumor at operation and with the freedom of that patient from incontinence. In only one patient was there any suggestion of dissociation of sensation, but the degree of sensory change was so small that no stress could be laid on this. Joint, pressure, and vibratory sensations were impaired in proportion to touch, temperature, and pain; pressure sensibility less noticeably than the other two. This helped us to differentiate a case of epiconus tumor which had been diagnosed *tabes dorsalis*. The patient's joint sensibility was so severely impaired that he was ataxic, but pressure sensibility was almost normal.

The degree of sensory loss of these patients was fairly in proportion to their motor weakness, but was not in proportion to the size of the tumor and the degree of involvement of surrounding structures (Cases 7 and 8). It was impossible to estimate the time of onset of sensory change in any of these cases, since the histories of none of them had been followed over a long period of time.

Fibrillary twitchings, usually indicative of anterior horn-cell involvement, were present in three cases. Two of these cases were extramedullary tumors showing that pressure on the cord will produce this sign without its infiltration.

**TENDINOUS REFLEXES.** As would be expected, the tendo Achillis reflex was absent or diminished in all the cases and the patellar reflexes were intact in only one. The cutaneous reflexes were interfered with in a few cases and helped greatly to estimate the highest level in the cord or the greatest number of roots involved by the tumor.

**SPINAL PUNCTURE.** This procedure must always be adopted to exclude the possibility of an inflammatory or syphilitic condition of the cauda. A "dry tap" is so rarely obtained that it is quite enough to suggest that something in the dural canal, probably a tumor, prevents the withdrawal of fluid. This was illustrated in Cases 4, 6, and 8, in which the canals were choked by large tumors. If the spinal puncture is performed by experts without securing fluid, suspicion of a tumor should be aroused. In Case 1 the xanthochromic and massive coagulation phenomena of Froin were present. This was enough to suggest a tumor above the site of the puncture, where it was found at operation. In Cases 5 and 7 the Nonne test was positive. The spinal fluid findings in Case 2 were equivocal, but in Case 1 they were frankly misleading. A large number of pus cells in the fluid led to a diagnosis of subdural abscess. The roentgen-ray examination of the lumbar spine and sacrum furnished little information beyond a lesion in the spine of Case 8, which afterward proved to be a spina bifida occulta.

**TROPHIC AND VASOMOTOR CHANGES.** In two cases there was evidence of edema of the lower limbs. This condition was discussed by Bailey, who quoted a case of Schmoll's in which the edema was so great that a laparotomy was performed to see if the inferior vena cava was obstructed. It was found that a caudal tumor was solely responsible for the edema.

**DIFFERENTIAL DIAGNOSIS.** Most of the patients presenting themselves for examination had definite physical signs of the disease and the diagnosis of some definite damage to the neural structures was comparatively easy. The differential diagnosis of causes of damage other than by tumor was not so easy. There were few patients, however, who had short histories; the majority of them had suffered intense pain for many months without a diagnosis being attempted. It is possible that for a long time before their arrival at the Clinic sufficient evidence might have been obtained to make diagnosis possible, and an early operation would have saved them months of agony and a final hopeless prognosis.

Every writer on this subject has deplored the frequency with which these tumors masquerade under a diagnosis of double sciatica, myositis or neuromuscular pain without any attempt being made to exclude the presence of a tumor. Even if there are no signs of tumor a long history of pain in a definite area should be sufficient to warrant the patient being kept under close observation. It is only by the recognition of early signs and their proper valuation

that a large number of patients may be saved from permanent paralysis or death. Further, the differentiation of tumor from other conditions is at times difficult. The intense constant pain is usual. This is sufficient evidence for the rejection of degenerative processes such as spinal bifida occulta, although this was an associated condition in Case 8. Elsberg operated in a case of spina bifida in 1908 and the patient developed a lipoma requiring laminectomy in 1910. Fuchs, in 1909, coined a term, myelodysplasia, to cover all sorts of congenital anomalies of the lower portion of the central nervous system. The most prominent symptoms were enuresis, sensory disturbances, and weakness of the lower limbs. Spiller, in 1916, reviewed this article and made more clear our conception of what may be included under this term. The sensory changes, weaknesses and atrophy of the lower extremities suggest tumor, but a careful search and roentgen-ray examination disclose such anomalies as spina bifida occulta, hypertrichosis over the skin of the sacral area, lipomas of the sacrum and associated stigmas of maldevelopment. Closely linked to this conception, if not included in it, is the abiotrophia of Gowers. It may start in the second or third decade of life and frequently cause strong suspicion of a progressive lesion-like tumor. The absence of pain, the long slow development, perhaps dating from earliest childhood, prevents such a diagnosis.

Hypertrophic arthritis of the lumbar spine with root pressure from bone overgrowth simulates tumor closely. A case of this kind was described by Bailey, in which, following an old injury, the patient developed pain, progressive weakness, and other symptoms suggesting a tumor compressing the lower segments of the cord. Laminectomy revealed granulations on the dura mater and bony overgrowth compressing the cord.

Tuberculous or syphilitic meningoradiculitis has to be excluded and all possibility of syphilis in the patient sought for. Laignel-Lavastine and Verliac described a case of the latter disease involving only half of the caudal roots, constituting an almost exact hemileSION. No similar instance was found in our records.

Toxic neuritis of the cauda equina, first described by Kennedy, Elsberg and Lambert in 1914, is difficult to distinguish from tumor. These authors presented the records of five cases, all progressive in type, and the course of illness in two was as long as two years. Their full description of the disease makes it evident that differentiation from tumor would be very difficult. Reynolds, in 1919, gave a full report of a similar case with a history as long as eight years, and the findings at operation were much the same as in the other five cases, namely, that the caudal roots were swollen, discolored, congested, and matted together.

I found the record of a patient in the Mayo Clinic who had been operated on for caudal tumor with very similar findings. The his-

tory dated back six years. The patient had pain, incontinence, and saddle anesthesia. The disease was progressive. Operative procedure did not reveal tumor but the caudal roots were swollen and congested. The suggestion of tumor was very strong and the diagnosis could hardly have been avoided. The spinal fluid was normal in this case.

Sacral tuberculosis may give rise to symptoms and signs like tumor, but in such cases the roentgen ray should aid in the diagnosis.

**LOCALIZATION OF TUMORS.** Before discussing this phase of the subject it may be well to consider a case that but for a rectal examination would have been diagnosed as caudal tumor.

**CASE 9 (313623).** Mr. J. J. F., an emaciated anemic man, aged sixty years, came to the Clinic, April 13, 1920, complaining of incontinence of urine, constipation, and pain in the back of his legs. Twelve months before he had noticed severe pain in and around the anus. He became constipated, which rapidly became more and more severe. Nine months before the pain had spread to the posterior aspect of the thigh and four months before his sexual power failed. He became incontinent of urine nine months after the onset, and a little later he lost rectal control. Eleven months after the onset he noticed an anesthesia and analgesia over the buttocks and posteromedial aspect of the thigh. His pain was relieved by walking around; he called it a "sharp rheumatic" pain. He had no knowledge of the passing of urine and could neither start it nor stop it. He had to dig out impacted feces unless they became liquid, then he was unconscious of their passage.

Examination showed a well-marked anesthesia corresponding to the fourth and fifth sacral segments, with some disturbance of sensations in the skin supplied by the third sacral segment (Fig. 6). All other areas were normal. There was no muscular weakness and the Achilles reflexes were only slightly diminished. Anal and bulbocavernous reflexes were absent and the spinal fluid was normal. Bladder and rectal control was absent. By digital examination of the rectum a large, hard, fixed tumor, rounded, with convex surface anteriorly about 8 cm. across, was found adherent to the anterior surface of the sacrum. It protruded into the rectum, but did not seem to arise therefrom. Several roentgenograms of the sacrum revealed nothing of note.

Before the position of the growth in this case was made manifest the signs and symptoms gave the picture of a tumor which might be in any of four separate and distinct positions. (1) An intramedullary tumor confined to the conus medullaris; (2) a tumor arising in the filum terminale, just as it arises from the tip of the conus; (3) a tumor arising from the same structure low in the sacral canal, and (4) a tumor in the pelvis. A tumor in the first position would destroy the third, fourth, and fifth sacral and the coccygeal

segments, a tumor in the second and third positions would press on or involve the roots of the same segments either in the lumbar canal or sacral canal, and finally, a tumor in the pelvis would press on and destroy the same roots after they emerged from the sacral foramina and had formed plexuses, destroying at the same time the ganglia and plexuses of the sympathetic system. The rectal examination demonstrated at once a tumor in the latter position.

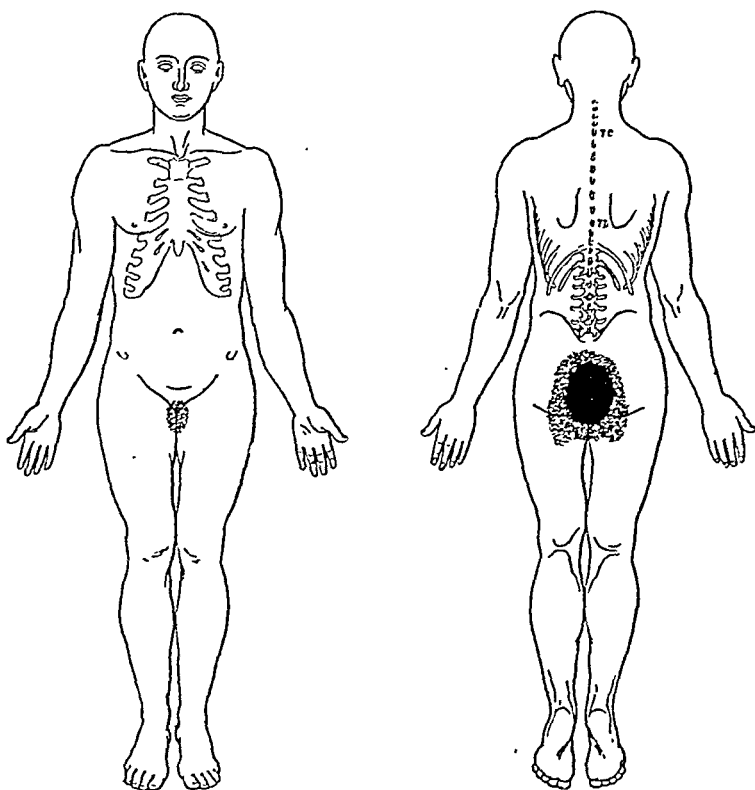


FIG. 6.—Case 9 (313623). Complete incontinence of urine and feces. Intrapelvic tumor involving the sacral nerve roots.

Many writers have endeavored to tabulate the differences between conus and caudal tumors, but a glance at the cases herein described will show the difficulty of being sure whether the tumor is intramedullary or is growing from the caudal roots. A tumor of this region follows no laws and selects its own path. A caudal tumor, as in Case 1, may press on the conus and produce signs of intramedullary damage such as fibrillary twitching. On the other hand a tumor originally intramedullary may spread from there to the roots and, as in Case 6, produce the intense pains associated with root tumors. Jacobsohn, in a paper on this subject, described a case in

which the diagnosis between conus and caudal tumor was impossible and a laminectomy showed the cauda intact. Necropsy showed a sarcoma of the dura compressing the conus on the right side. He insists on the difficulty of diagnosis in similar cases.

In Case 6, because the fourth and fifth lumbar and the first and second sacral segments were damaged, with preservation of the third, fourth, and fifth sacral segments, a diagnosis of intramedullary growth was made, as in a caudal lesion the central fibers could hardly have escaped. They are often the first to be affected.

In the early stages of growth of the tumor the exact localization may be impossible. It is only by careful and close study of each individual case on its own merits, and by applying the results of past experience, that some idea of the position, extent, and nature of the tumor may be ascertained.

**Summary.** 1. Tumors of the cauda equina, conus and epiconus are not rare. Of thirty-three patients with tumors of the spinal cord operated on since 1916, eight had tumors in one of these areas.

2. The course of the disease to the time of operation was relatively long, the longest being eight years and the shortest five months.

3. The signs and symptoms are characterized, on the whole, by pain and weakness of the lower extremities and perianal or saddle anesthesia, with loss of control of the bladder and rectum.

4. The pain may precede the other signs for many months; intermittent at first, it is constant toward the end. Movement usually relieves it and a sitting position is felt by the patient to be the most comfortable.

5. Sphincteric disturbance may be absent, although other signs are well marked.

6. Spinal puncture is a valuable aid, primarily to exclude other diseases; it may also give a hint of the condition of the dural canal.

7. While diagnosis of tumor somewhere in the lowest segments of the cord is comparatively simple, its exact localization is often impossible or extremely difficult, and a surprising degree of involvement of structures is often present with few signs and symptoms to correspond.

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## ERYTHROPOIETIC ACTION, CUMULATIVE EFFECT AND ELIMINATION OF GERMANIUM DIOXIDE.

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THE importance of germanium dioxide as an erythropoietic agent has recently been established by the investigations of Hammett, Nowrey and Müller. This experimental work was conducted at the Wistar Institute of Anatomy and Biology, Philadelphia, and the article treating of the results appeared in the *Journal of Experimental Medicine*, February, 1922.

The abstract of this article pointed out that the tests were conducted on albino rats. The results of experimentation showed that "there took place, as the result of the administration of the compound, a marked and statistically valid rise in the number of the erythrocytes. There was no corresponding leukemia. Autopsy of the treated rats showed, on gross inspection, that the bone-marrow and liver probably participate in the reaction which results in the erythropoiesis."<sup>1</sup>

As an outgrowth of the above-mentioned work the authors of this paper have conducted several series of tests, which work was

<sup>1</sup> Hammett, Nowrey and Müller: Erythropoietic Action of Germanium Dioxide, *Jour. Exper. Med.*, 1922, 35.

carried out on the guinea-pig, rabbit, dog and man. The investigation was undertaken with the purpose of finding out: (a) The erythropoietic action of germanium dioxide on animals other than the albino rat; (b) the toxic effect of large doses; (c) the cumulative effect of the compound in the system; (d) the elimination of the compound from the system.

**Previous Work with Germanium Dioxide.** A search of the literature shows that animal experimentation with germanium dioxide is comparatively a new field of work. Müller in his article in the *Journal of the American Chemical Society*, which deals with the determination of the atomic weight of germanium, has given methods for the preparation of germanium compounds in a high state of purity.<sup>2</sup>

The next work with germanium was that dealing with "The Relative Toxicity of Germanium and Arsenic in the Albino Rat." This work was conducted by Hammett, Müller and Nowrey, and the publication of their findings appeared in the *Journal of Pharmacology and Experimental Therapeutics*. Primarily, this work was suggested by the close relationship existing between arsenic and germanium in their respective positions in the periodic system, in which they are adjacent in series. The solubility of germanium dioxide in water is the most striking connection between this oxide and the oxides of arsenic, in which respect germanium departs from the behavior of the other elements in Group IV of the periodic system and resembles arsenic, holding the adjacent position in Group V.

The results of the findings of the above authors showed that "germanium dioxide can be administered subcutaneously in the albino rat in doses up to 180 mg. per kilo of body weight with no harmful effects, whereas arsenic exhibits fatal results in a ratio of 8 mg. per kilo of body weight. Therefore, germanium does not possess a toxicity for the living animal organism such as exhibited by arsenic."<sup>3</sup>

Later came the work by the same authors dealing with the erythropoietic action of germanium dioxide, previously mentioned in this paper.

As far as the authors of the present paper can ascertain these above-mentioned articles are the only reports of work thus far conducted in connection with the physiological action of germanium.

**Present Investigations.** The germanium dioxide used throughout the present work was a portion of the original atomic weight material belonging to one of us.

<sup>2</sup> Müller, J. H.: Atomic Weight of Germanium, *Jour. Am. Chem. Soc.*, 1921, 43, 1083.

<sup>3</sup> Hammett, Müller and Nowrey: Relative Toxicity of Germanium Dioxide and Arsenic for the Albino Rat, *Jour. Pharmacol. and Exper. Therap.* (Accepted for publication.)

The authors wish to state that the solubility of germanium dioxide in water has been redetermined by them, and it has been shown that a freshly prepared solution has a strong tendency to supersaturation and colloid formation. Such a supersaturated solution at 26° C. contains 0.006632 gm. of germanium dioxide per cc, but on long standing deposits a considerable quantity of the hydrated oxide. Solutions of this concentration were at first employed in this experimental work, but later were substituted by a stable saturated solution containing 0.004684 gm. of germanium dioxide per 1 cc, representing the true solubility of the pure oxide in water.

The laboratory animals used in all the tests were kept in individual wire cages and were held under observation for one week preceding experimental work, in order for them to become acclimated to their new conditions. During this period, as well as during the period of experimentation, the amount and character of the food were controlled, carrots, cabbage and water being given. Weight determinations were likewise made during the entire period at intervals of twenty-four hours.

All injections were made with a sterilized Luer 10 cc hypodermic syringe.

All blood counts were made in a blood-counting chamber having the Zappert-Neubauer type of ruling. The technic employed in making the blood counts was that as outlined in Stitt's *Practical Bacteriology Blood Work and Parasitology*.<sup>4</sup>

**Erythropoietic Action of Germanium Dioxide.** A preliminary test was run on a series of eight guinea-pigs to determine:

1. Whether an appreciable increase in erythrocyte count followed dosage with germanium dioxide.

2. Whether there was an accompanying increase or decrease in body weight.

3. Whether there was an increase in hemoglobin content.

4. Whether there was a difference between method of administration and increase in red blood cell count.

The germanium dioxide used in testing this series contained 6.632 mg. of germanium dioxide per 1 cc. The amount of germanium dioxide given was calculated on the basis of 100 mg. per kilo of body weight.

Of this series 3 animals received subcutaneous injections, 3 animals received intraperitoneal injections and 2 were used as controls.

The results of this preliminary series of tests showed that:

1. There was an appreciable increase in erythrocyte count, since it was possible to demonstrate, in all the animals treated, a rise of at least 1,000,000 over the normal count.

<sup>4</sup> Stitt, E. R.: *Practical Bacteriology, Blood Work and Parasitology*, sixth edition. P. Blakiston's Son Co., pp. 249-252.

TABLE I.—SHOWING THE ERYTHROPOIETIC ACTION OF GERMANIUM DIOXIDE IN A SERIES OF FOUR GUINEA-PIGS.

Days.	Animal No. III.			Animal No. III.			Animal No. IV.			Animal No. IV.		
	Dose of GeO <sub>2</sub> in mg.	Erythrocyte count in c.mm.	Weight of animal in gm.	Dose of GeO <sub>2</sub> in mg.	Erythrocyte count in c.mm.	Weight of animal in gm.	Dose of GeO <sub>2</sub> in mg.	Erythrocyte count in c.mm.	Weight of animal in gm.	Dose of GeO <sub>2</sub> in mg.	Erythrocyte count in c.mm.	Weight of animal in gm.
0	27.6356	4,590,000	371	26.4988	4,420,000	362	30.4460	5,000,000	415	26.4988	4,520,000	365
1	.....	5,290,000	352	.....	4,650,000	342	.....	5,140,000	431	.....	5,210,000	370
2	.....	5,520,000	362	.....	5,070,000	330	.....	5,320,000	427	.....	6,160,000	383
3	.....	5,120,000	366	.....	5,240,000	336	.....	5,340,000	429	.....	5,200,000	390
4	.....	4,440,000	378	.....	4,800,000	336	.....	5,190,000	450	.....	5,520,000	384
5	.....	4,570,000	396	.....	5,110,000	336	.....	5,160,000	453	.....	5,870,000	391
6	46.84	4,570,000	345	.....	4,470,000	336	.....	5,100,000	460	.....	5,720,000	371
7	.....	4,990,000	340	.....	5,340,000	330	46.84	5,100,000	463	.....	4,960,000	408
8	.....	4,930,000	340	.....	5,460,000	354	.....	6,600,000	400	.....	4,950,000	407
9	.....	5,160,000	360	46.84	4,580,000	350	.....	5,960,000	353	46.84	4,910,000	405
10	.....	5,740,000	365	.....	5,280,000	345	.....	5,690,000	346	.....	5,500,000	367
11	.....	5,670,000	375	.....	4,810,000	352	.....	6,880,000	330	.....	6,050,000	370
12	.....	5,040,000	375	.....	4,760,000	355	.....	6,430,000	325	.....	5,690,000	380
13	.....	.....	.....	.....	4,570,000	357	.....	5,400,000	297	.....	5,830,000	398
14	.....	.....	.....	.....	4,930,000	352	.....	.....	...	.....	6,060,000	404
15	.....	.....	.....	.....	5,000,000	368	.....	.....	...	.....	4,920,000	397

2. As regards the body weight the animals receiving but one dose based on 100 mg. per kilo of body weight showed no change or a slight increase in body weight, whereas those given more than one dose on successive days showed a decrease in body weight, from which they gradually recovered after dosing was discontinued.

3. Accompanying an increase of 1,000,000 in erythrocyte count there was an increase in hemoglobin approximating a rise of 8 to 10 per cent above the normal hemoglobin reading.

4. Since all animals treated showed a rise in the erythrocyte count, which rise showed no variation between subcutaneous and intraperitoneal injections, the authors concluded that the mode of administration does not affect the erythropoietic action of the germanium dioxide.

**A. Erythropoietic Action of Germanium Dioxide in Guinea-pigs.** Following the preliminary series a more detailed series of tests was run on 4 guinea-pigs, observations being made at intervals of twenty-four hours as regards body weight and erythrocyte count.

In this series the dose was administered intraperitoneally.

The normal erythrocyte count and weight of the animal was taken just prior to the initial dose.

The germanium dioxide used in this series was a solution containing 4.684 mg. per 1 cc.

Table I shows the results of this experimental work:

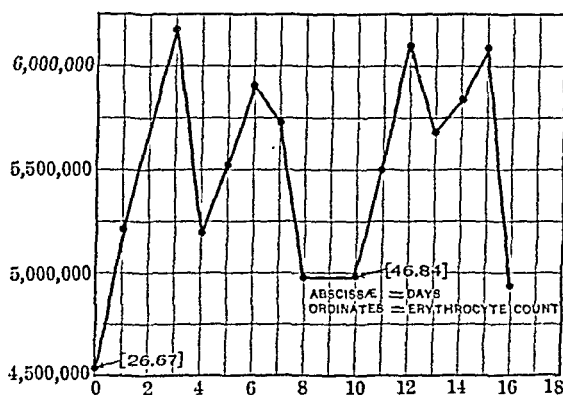


CHART I.—Curve showing the erythropoietic action of germanium dioxide in a guinea-pig. Two doses of  $\text{GeO}_2$  given intraperitoneally; each cc of solution = 4.68 mg.  $\text{GeO}_2$ . Arrows above indicate days on which doses were received, and bracketed numbers indicate the number of mgs. received on that particular day

Table I shows that following the administration of a dose based on 100 mg. per kilo of body weight there was (a) an accompanying rise in erythrocyte count, (b) there was a change in the body weight in the case of Nos. III<sub>1</sub> and III<sub>2</sub> there occurred a slight decrease in body weight at first followed by a rise above the weight taken just prior to the initial dose; in case of Nos. IV<sub>1</sub> and IV<sub>2</sub> a gradual

increase in body weight was seen. However in all 4 animals when the amount of dose was doubled there was noted a decrease in body weight followed by an increase in 3 of the animals, which increase was above the first weight taken.

This rise and fall in the erythrocyte count can best be shown if plotted graphically. Chart I is the erythrocyte curve of animal No. IV<sub>2</sub>, the weights and erythrocyte counts of which are given in Table I.

**B. Erythropoietic Action of Germanium Dioxide in a Rabbit.** For this experiment a 2479 gm. male rabbit was used. This rabbit was given an intraperitoneal injection of germanium dioxide containing 4.684 mg. per 1 cc. In other words the rabbit received 234.2 mg., which dose based upon kilo of body weight is 94.4 mg. per kilo. Following this injection records of the weight and erythrocyte count were made for a period of two weeks at approximately twenty-four-hour intervals. Table II shows the results obtained:

TABLE II.—ERYTHROPOIETIC ACTION OF GERMANIUM DIOXIDE  
IN A RABBIT WHICH HAD RECEIVED 234.2 MG. OF  
GERMANIUM DIOXIDE IN ONE DOSE.

Days.	Weight of rabbit in grams.	Erythrocyte count in cubic millimeter.
0	2479	5,350,000
1		
2	2458	5,910,000
3	2375	6,170,000
4	2325	6,430,000
5		
6	2289	5,830,000
7	2504	6,730,000
8	2330	6,210,000
9	2215	6,890,000
10		
11	2390	7,120,000
12	2320	6,090,000
13	2329	6,440,000
14	2395	5,950,000
27	....	6,030,000

Table II shows that accompanying a single dose there is a rise and fall in the erythrocyte count which extends over a period of two weeks, reaching its maximum on the ninth day, an increase of 1,540,000 over the normal count. On the fourth and thirteenth days are seen increases of 1,000,000 over the normal count. At the end of the second week the count becomes a constant, as was proved by allowing thirteen days to elapse before the final count. This determination showed no appreciable rise.

Chart II, which is the graphic chart of erythrocyte counts of the rabbit demonstrates a similar condition following the dose of germanium dioxide to that exhibited in the guinea-pig in Chart I.

The dotted line in the curve indicates the lapse of thirteen days.

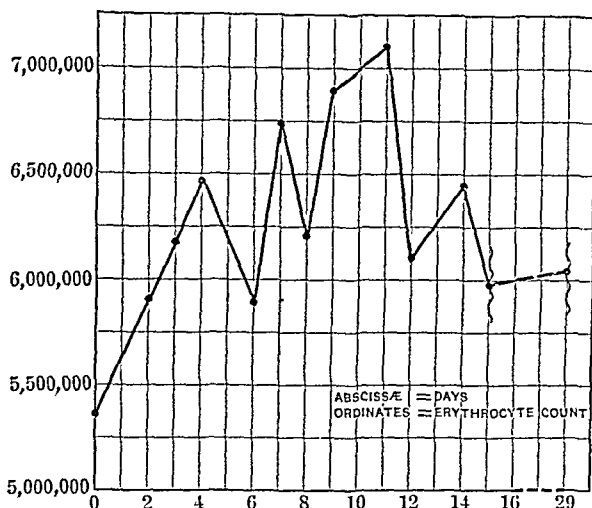


CHART II.—Curve showing erythropoietic action of germanium dioxide in a rabbit. One dose of  $\text{GeO}_2$  given intraperitoneally on 0 day, 50 cc of a solution being given which contain 4.684 mg. of  $\text{GeO}_2$  per cc.

**C. Erythropoietic Action of Germanium Dioxide on a Dog.** A St. Bernard dog, aged ten years, weighing about 62 kg., was kept under observation for forty-eight days, during which time doses of germanium dioxide were given subcutaneously in the region of the breast at stated intervals, and the erythrocyte count was made every twenty-four hours.

Table III and the accompanying graphic chart show the nature and results of this experimental work.

Before interpreting the results demonstrated in Table III and Chart III the authors wish to state that the dog gave an initial count of 2,000,000 below the average normal count, which count for a dog is 6,500,000.<sup>5</sup> This subnormal erythrocyte count can possibly be attributed to the age of the dog.

As the result of continued dosing in the first nine days there was seen an increase in red blood corpuscles reaching a maximum on the fourth day after the first dose was received, which increase was 3,150,000 over the initial count. On the fifth day a decrease was demonstrated, followed by a recovery on the sixth day. Accompanying this continued dosing there was seen a fluctuating rise and fall in the curve.

Following the discontinuance of the dose on the ninth day the count gradually rose, reaching on the seventeenth day, which is eight days after discontinuance of the dose, a maximum comparable to that reached on the fourth day. Without any further dosing the erythrocyte count dropped, reaching its lowest point on the twenty-first day, eleven days after the cessation of dosing.

<sup>5</sup> Plimmer, R. H. A.: *Practical Organic and Biochemistry*, Longmans, Green & Co., 1920, p. 473.

Again a rise was demonstrated, and on the twenty-sixth day, or sixteen days after the last dose, a second maximum was reached which was just 1,000,000 less than the first. Following this second rise the erythrocyte count gradually approached the normal reading, becoming more or less constant at a count about 1,000,000 above the initial count.

TABLE III.—SHOWING ERYTHROPOIETIC ACTION OF GERMANIUM DIOXIDE IN A DOG. TOTAL DOSE = 1265.7 MG.

Days.	Erythrocyte count in cubic millimeter.	Subcutaneous dose of germanium dioxide in cubic centimeters of solution.	Dose of germanium dioxide in milligrams.
0	4,550,000	17.4	115.4
1	5,390,000	15.5	102.8
2	6,000,000	15.3	101.5
3	6,700,000	15.5	102.8
4	7,700,000	15.3	101.5
5	6,390,000	15.3	101.5
6	7,320,000	15.3	101.5
7	7,200,000	15.3	101.5
8	.....	15.3	101.5
9	7,480,000	15.3	101.5
10			
11	7,210,000		
12	6,210,000		
13	6,300,000		
14	6,400,000		
15	6,500,000		
16			
17	7,800,000		
18	7,300,000		
19	6,600,000		
20	6,340,000		
21	5,140,000		
22			
23	5,450,000		
24			
25	6,590,000		
26	6,750,000		
27	5,900,000		
28	5,700,000		
29	5,790,000		
30	5,000,000		
31	5,100,000		
32	5,060,000	50.0	234.2
33	5,980,000		
34	5,660,000		
35	6,760,000		
36			
37	6,630,000		
38	6,970,000		
39			
40	6,100,000		
41	5,750,000		
42			
43	6,250,000		
44	5,600,000		
45			
46	5,660,000		
47			
48	5,650,000		
63	6,250,000		



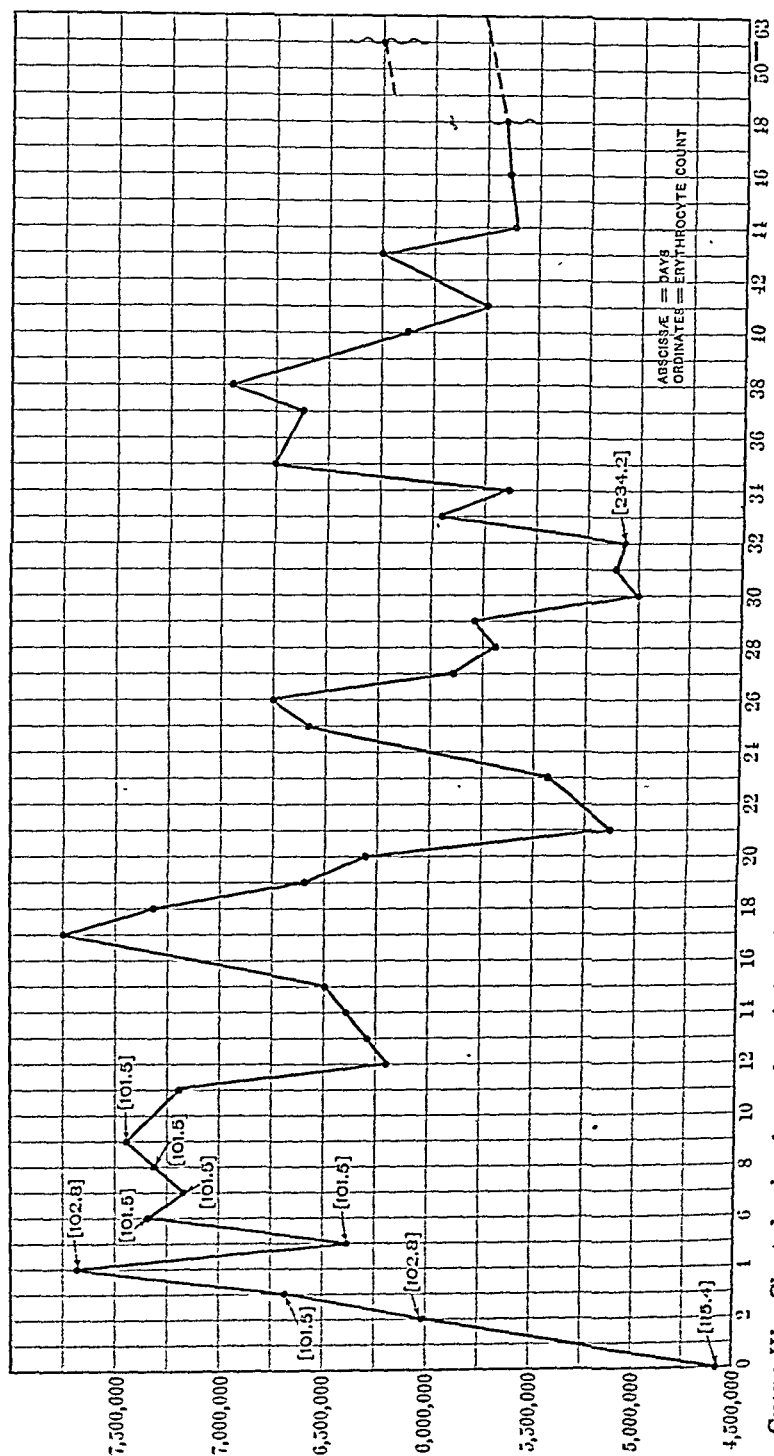


CHART III.—Chart showing the erythropietic action of germanium dioxide in a dog. Doses of  $\text{GeO}_2$  given subcutaneously. Arrows above indicate days on which doses were received, and bracketed numbers indicate the number of mgs. received on that particular day.

When the count was demonstrated as being a constant a large dose of 234.2 mg. of germanium dioxide in solution was injected into the dog. Following this dose there can readily be seen by referring to Curve III that a rise and fall in erythrocyte count occurred comparable to that demonstrated in previous continued dosing.

Summing up the above results it has been demonstrated that one large dose shows the same effect as regards increase in erythrocyte count that continued small doses on successive days produce. Also that the reaction of germanium dioxide is rapid, requiring four days to reach its maximum and approximately two weeks following discontinuance of the dosage before the erythrocyte count becomes a constant.

By referring to Chart III and Table III it is seen that the count obtained on the sixty-third day indicates a rise over that made on the forty-eighth day. However, the interesting fact is that this last count is approximately that of a normal dog.<sup>6</sup>

**D. Erythropoietic Action of Germanium Dioxide in a Man Aged Thirty-nine Years.** In carrying out this phase of the work the dose of germanium dioxide was administered through the mouth, an aqueous solution of the dioxide being taken on an empty stomach in each instance, one-half hour before a meal. Prior to the initial dose the weight and red blood cell count were taken.

Observations of the erythrocyte count and body weight were made on this individual over a period of forty-two days. Table IV and Chart IV give a consideration of the work done and the results obtained.

Both Table IV and Chart IV show that the rise and fall in the erythrocyte count, accompanying and following dosage of germanium dioxide in man, is comparable with that exhibited in the case of laboratory animals. At the end of the second week following the discontinuance of the dose the count became a constant, further confirmed by a count made fifteen days later. This is shown on the chart by a dotted line.

In addition the results for man show that a dose absorbed through the stomach produces the same effect in increasing the erythrocyte count as subcutaneous and intraperitoneal injections did in the case of the laboratory animals.

In summing up the work on the erythropoietic action of germanium dioxide the following conclusions have been drawn.

1. Following a dose of germanium dioxide based upon 100 mg. per kilo of body weight there is a marked rise in erythrocyte count.
2. Following doses of germanium dioxide the authors were able to demonstrate in each case a rise in red blood cell count of at least 1,000,000 above the count obtained just preceding the first dose.

<sup>6</sup> Loc. cit.

The maximum erythrocyte count obtained was a rise of 3,000,000 in the case of the dog, the initial count of which was below normal.

3. Following a single dosage there follows a rise and fall in the erythrocyte curve explainable probably on the grounds of periodicity, a certain linking up of the compound, causing a stimulation of the blood-producing organs, followed by the rapid production of erythrocytes. This opinion is supported by the hyperemic condition of the bone-marrow, plainly seen on gross examination, at autopsy, of the long bones of all animals injected.

TABLE IV.—SHOWING THE ERYTHROPOIETIC ACTION OF GERMANIUM DIOXIDE IN A MAN. DOSES TAKEN THROUGH THE MOUTH. TOTAL DOSE = 2408.7 MG.

Days.	Erythrocyte count in cubic centimeter.	Dose of germanium dioxide in cubic centimeter of solution.	Dose of germanium dioxide in milligrams.	Body weight in kilos.
0	5,000,000	15.3	110.5	61.01
1	6,550,000	15.3	110.5	61.00
2	6,310,000	30.6	203.0	61.69
3	6,140,000	30.6	203.0	61.78
4	5,900,000	30.6	203.0	61.46
5	6,000,000	30.6	203.0	61.91
6	6,010,000	30.6	203.0	
7	6,220,000	30.6	203.0	61.82
8	5,580,000	30.6	203.0	61.82
9	5,300,000	....	.....	62.00
10	.....	....	.....	62.05
11	5,900,000	....	.....	62.20
12	6,270,000			
13	5,850,000	....	.....	61.91
14	5,330,000	....	.....	61.90
15	4,900,000	30.6	143.2	61.40
16	5,140,000	30.6	143.2	61.23
17	5,220,000	30.6	143.2	61.30
18	.....	....	.....	61.70
19	5,350,000	....	.....	61.75
20	5,820,000	....	.....	61.75
21	5,600,000	....	.....	62.14
22	5,220,000	....	.....	61.90
23	5,560,000	....	.....	62.10
24	5,100,000			
25	4,910,000			
26	5,010,000	50.0	234.2	61.75
27	5,650,000	26.0	121.8	61.70
28	6,510,000	....	.....	61.69
29	5,890,000	....	.....	61.69
30	.....	....	.....	61.69
31	5,430,000			
32	5,540,000			
33	.....			
34	5,190,000			
35	5,460,000	....	.....	61.68
36	.....	....	.....	61.68
37	5,200,000	....	.....	61.68
38	5,540,000	....	.....	61.70
39	.....	....	.....	61.80
40	5,460,000			
41	.....	....	.....	61.90
42	5,500,000	....	.....	62.00
57	5,550,000			

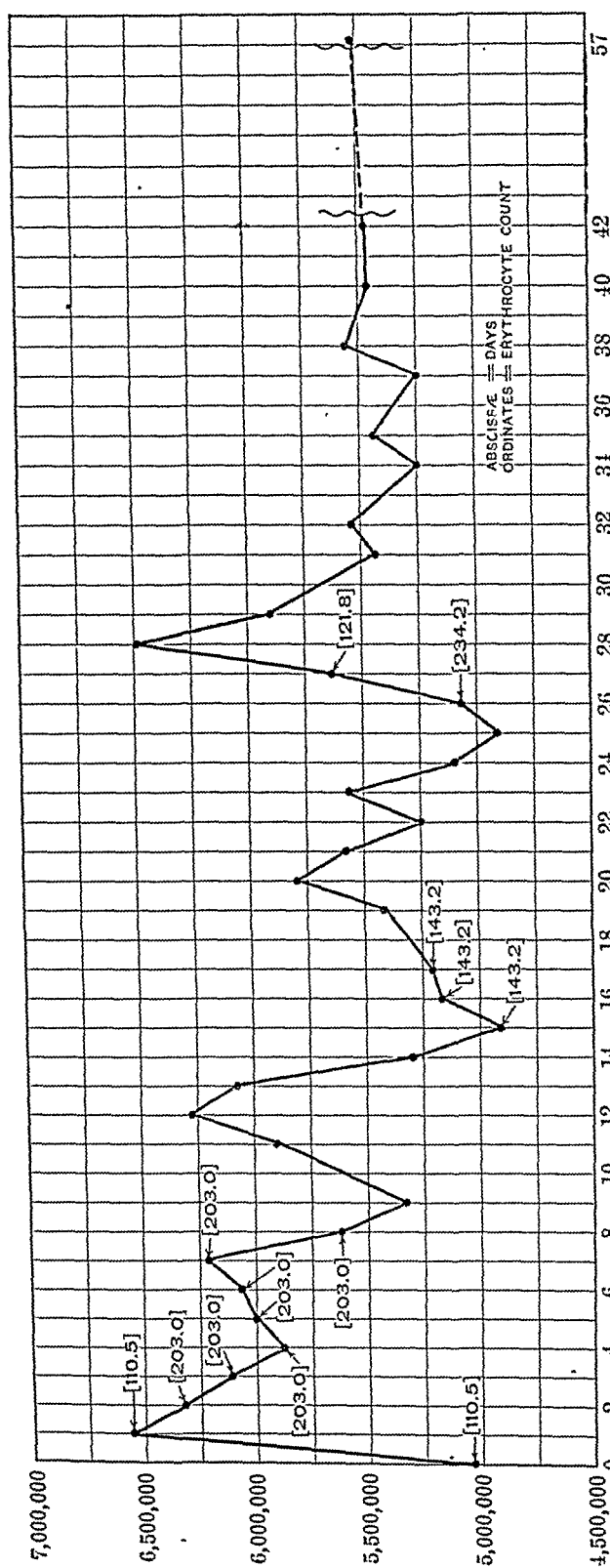


CHART IV.—Chart showing the erythropoietic action of germanium dioxide in man. Doses of  $\text{GeO}_2$  taken through the mouth. Arrows indicate days on which doses were received, and bracketed numbers indicate the number of mgs. received on that particular day.

**Toxic Action of Germanium Dioxide.** Work done at the Wistar Institute of Anatomy and Biology on the toxicity of germanium dioxide in the albino rat was concerned chiefly with the administration of small doses, the largest dose given being 180 mg. per kilo of body weight which represented in actual quantity not more than 34 mg. per animal.<sup>7</sup>

The writers of this paper have in their work used in the various phases of this problem as much as:

Guinea-pig, 73.5 mg.

Rabbit, 234.2 mg.

Dog, 1265.7 mg.

Man, 2408.7 mg.

which doses showed no apparent toxic effect.

These amounts, however, were not given in one dose but were extended over a period of several days, with intervals elapsing. Hence the factor of elimination enters in, discussed later in this article, which work shows that germanium dioxide is rapidly eliminated from the system.

In testing out the toxic effect of germanium dioxide a series of 3 guinea-pigs was injected intraperitoneally with the germanic acid solution.

Pig A received as an initial dose 39.78 mg. of germanium dioxide.

Pig B received as an initial dose 53.04 mg. of germanium dioxide.

Pig C received as an initial dose 66.32 mg. of germanium dioxide.

The subsequent doses received by each animal were the same as the initial dose received.

Table V shows the result of administration of these quantities.

The result of this experimental work shows that the fatal dose is between 238.68 mg. and 265.20 mg. of germanium dioxide, since a pig receiving 238.68 mg. was unaffected and all receiving as much as 265.20 mg. died.

Accompanying the large doses received by these animals there was a marked decrease in body weight. At autopsy no gross pathological changes were noted except a marked hyperemic condition of the bone-marrow. Moreover, in the tests conducted to determine the erythropoietic action of germanium dioxide it was noticed that when a large dose was given there was a retardation in the increase of red blood corpuscles and an accompanying decrease in the body weight, therefore it can be concluded that germanium dioxide does have a toxic effect if taken in very large doses.

Calculating on the basis of per kilo of body weight it was found from the preceding experiment that 265 mg. of germanium dioxide proved fatal for the 3 guinea-pigs injected. Since the heaviest of these animals weighed 465 gm. we can assume that the lethal dose

<sup>7</sup> Hammett, Müller and Nowrey: Relative Toxicity of Germanium Dioxide and Arsenic for the Albino Rat, Jour. Pharmacol. and Exper. Therap. (Accepted for publication.)



of germanium dioxide is 265 mg. Therefore, per kilo of body weight the fatal dose would be 586 mg. of germanium dioxide.

To substantiate this conclusion a series of 4 guinea-pigs were injected, basing the dosage on 586 mg. of germanium dioxide per kilo as fatal.

TABLE VI.—SHOWING RESULTS OF FATAL DOSING WITH GERMANIUM DIOXIDE.

Animal.	Body weight in grams.	Dose of germanium dioxide in cubic centimeters.	Dose of germanium dioxide in milligrams.	Results.
Guinea-pig W <sub>1</sub> . .	322	40.6	190.17	Death within 18 hours after dose.
Guinea-pig W <sub>2</sub> . .	319	40.2	188.29	Death within 18 hours after dose.
Guinea-pig X <sub>1</sub> . .	380	47.8	223.89	Death within 18 hours after dose.
Guinea-pig X <sub>2</sub> . .	380	47.8	223.89	Death within 18 hours after dose.

Table VI shows that following one large dose, supposedly the approximate lethal dose, all 4 guinea-pigs died within eighteen hours.

Therefore, between 500 and 600 mg. per kilo of body weight is toxic for the guinea-pig. Also this amount given in one large dose has the same effect as a series of smaller doses given on successive days See Table V. Hence the toxic action is not due to cumulative effect. In all cases in which toxic action was observed an overstimulation of the blood-producing organs was seen, for in all animals that died, both in this last series as well as in the previous series, on gross examination, the bone-marrow showed a marked hyperemic condition and was dark red and seemed to be in a state of coagulation, this condition being most marked at the joints of the long bones.

It was thought necessary by the authors to ascertain whether the injection of such a large volume of solution of slightly less than isotonic concentration might have contributed to the fatal effects produced in the preceding series of guinea-pigs, hence a solution of pure sodium chloride of the same tonicity as that of the-germanic acid was injected into 2 control guinea-pigs. This volume of salt solution had no apparent affect upon the animals injected.

**Cumulative Effect and Elimination of Germanium Dioxide.** Since this phase of the problem requires the employment of a method whereby chemical analysis of animal tissues and excreta for germanium dioxide may be made, the authors wish to here state in detail the methods employed by them in making such chemical analyses.

**Quantitative Analysis of Animal Tissues and Excreta for Germanium Dioxide.** The general procedure was essentially the same as that

employed by Buchanan<sup>8</sup> in the analysis of inorganic mixtures bearing germanium, advantage being taken of the elaboration of this method as detailed in the later work of Dennis and Papish.<sup>9</sup>

This method is based upon the volatility of germanium tetrachloride from an aqueous hydrochloric acid solution in a current of chlorine.

As no examination of organic matter for germanium content has been reported, the authors of this paper found it necessary to make investigation concerning the preliminary treatment of the animal organs and excreta, so that practically all the germanium could be recovered from relatively large masses of organic matter.

The following procedure was finally adopted as most satisfactory:

In the case of urine and fecal material it was necessary to treat the collected samples with an excess of sodium hydroxide to fix the germanic acid content before evaporation and ignition. Approximately 10 gm. of caustic soda were added for each 300 cc sample of urine; in the case of the fecal material this was thoroughly moistened with a concentrated solution of sodium hydroxide immediately following the collection of the sample. Such materials cannot otherwise be evaporated to dryness and ignited without loss of germanium on account of the large amounts of chlorides always present.

The samples were evaporated to dryness under a hood and the dried residues were then heated in covered porcelain dishes to slightly above the charring temperature, care being exercised to avoid overheating the bottom of the dishes, and no attempt was made to burn off the residual carbon. At a low red heat in the well-covered dish the unburned porous carbon prevents the alkali from melting down and attacking the porcelain container. In the case of the urine residues especially a complete charring is desirable, as the less strongly heated residues cause much trouble by foaming when subsequently treated with hydrochloric acid.

The charred alkaline masses were next disintegrated in a little distilled water and neutralized with hydrochloric acid, and the whole rinsed into the distilling apparatus with a large excess of 1 to 1 hydrochloric acid. Usually the volume of the liquid subjected to distillation measured from 250 to 300 cc, and about two-thirds of this volume were driven over as distillate before interruption of the distilling operation. Further small portions of distillate were collected and examined for germanium dioxide as a check upon the complete removal of the tetrachloride.

Adequate condensing surface, thorough cooling of the water in the receiver, together with a safety water-trap to prevent loss of germanium chloride in the chlorine stream, were especially necessary

<sup>8</sup> Buchanan: *Jour. Indus. and Engin. Chem.*, 1916, 8, 535; 1917, 9, 661.

<sup>9</sup> *Jour. Am. Chem. Soc.*, 1921, 43, 2131.



in the estimation of small quantities of germanium in the large masses of organic matter present in these determinations.

In case of the animal organs, muscle and bone samples all were digested for twenty-four hours with concentrated hydrochloric acid in stoppered flasks (100 cc of concentrated hydrochloric acid for each 20 gm. of sample). After the addition of an equal volume of water the turbid mass was transferred to the distilling apparatus together with sufficient 1 to 1 hydrochloric acid to make the volume up to 250 cc chlorine slowly led through the system in the cold was then allowed to destroy most of the organic matter before the final distillation.

From this point the analysis of the samples of urine, fecal material and animal tissues were identical. The acid distillates in all these analyses contained not only dilute hydrochloric acid, chlorine and germanium chloride, but also appreciable quantities of chlorinated fatty esters resulting from the incomplete destruction of the organic matter by either the wet or dry methods. This was evidenced by the presence of minute oily particles or a small flocculent precipitate in the distillate.

The distillates were not filtered but treated directly with hydrogen sulphide under pressure to saturation in the cold. The precipitate, containing germanium sulphide, pure sulphur and chlorinated fatty compounds, was then removed by filtration and digested in alcohol acidified with hydrochloric acid and saturated with hydrogen sulphide. The germanium sulphide which remained insoluble was again filtered out and washed with pure alcohol containing hydrogen sulphide. The sulphide was now converted in the usual manner to dioxide, in which condition the germanium was weighed.

By the above method germanium dioxide can be detected in as small a quantity as 0.0002 gm.

It should be noted that the concentration of the hydrochloric acid used in these analyses is much greater than that recommended in the article by Dennis and Papish<sup>10</sup> on the separation and determination of germanium, but the special attention to acid concentration during distillation is only necessary in the presence of arsenic, which was not present in the material here analyzed.

In case of the presence of arsenic in animal tissues or excreta there are two methods which may be adopted for the determination of germanium:

METHOD I. The method given by Dennis and Papish.<sup>11</sup> A modified distillation method depending upon the maintenance of the arsenic in the pentavalent state in an atmosphere of chlorine, under which condition the arsenic remains non-volatile.

METHOD II. A separation of arsenic and germanium through the

<sup>10</sup> Loc. cit.

<sup>11</sup> Loc. cit.

difference in the behavior of their sulphides toward hydrofluoric acid.<sup>12</sup>

This latter method, in the opinion of the writers of this article, has decided advantage over Method I in the simplicity of manipulation.

**Cumulative Effect of Germanium Dioxide.** In order to determine whether there was any accumulation and localization of germanium dioxide in the various organs of the guinea-pig a 422-gm. animal was given 40 cc of germanium dioxide in 10 cc doses over a period of four successive days. Since each cubic centimeter of such a solution contained 6.632 mg. of germanium dioxide the animal received as a total dosage 264.8 mg.

On the fifth day the animal died and was posted, the lungs, liver, kidney, muscle and leg bones being removed and examined separately by the chemical procedure as outlined by the authors under the quantitative determination of germanium dioxide in the animal tissues.

Table VII shows the result of such analyses:

TABLE VII.—SHOWING THE RECOVERY OF GERMANIUM DIOXIDE FROM THE ORGANS OF A GUINEA-PIG WHICH HAD RECEIVED AN APPROXIMATE LETHAL DOSE OF THE COMPOUND. TOTAL DOSE OF GERMANIUM DIOXIDE RECEIVED, 264.8 MG.

Organs analyzed.	Amount of germanium dioxide recovered in milligrams.	Percentage of total dosage received.
Lung . . . . .	0.9	0.34
Liver . . . . .	1.4	0.53
Kidney . . . . .	1.1	0.41
Muscle . . . . .	0.5	0.19
Bone (legs) . . . . .	0.3	0.11
Total recovery . . . . .	4.2	1.58

From Table VII it is evident that the accumulation of germanium dioxide in the organs examined is small and the amount recovered due to the blood content of the organs at the time of analysis.

To confirm this statement another guinea-pig was injected intraperitoneally with a slightly smaller dose than the guinea-pig listed in Table VII. The injections in this second pig were given in the same way as the injection received by the guinea-pig of Table VII. On the fifth day following the first dose the animal was bled from the jugular vein while under an anesthetic. Nineteen grams of blood were obtained, which amount was approximately 30 per cent of the total blood content of the animal. Chemical analysis

<sup>12</sup> Müller, J. H.: Separation of Germanium and Arsenic, Jour. Am. Chem. Soc., 1921, 43.

for germanium dioxide was made of the blood and organs of this guinea-pig.

The results of this work appear in Table VIII:

TABLE VIII.—SHOWING RECOVERY OF GERMANIUM DIOXIDE FROM BLOOD AND ORGANS OF GUINEA-PIG WHICH HAD RECEIVED SLIGHTLY LESS THAN LETHAL DOSE. TOTAL DOSE OF GERMANIUM DIOXIDE RECEIVED, 187.3 mg.

Analyses made.	Amount recovered of germanium dioxide in milligrams.	Percentage of total dosage received.
Blood 19 gms. collected . . . . .	2.8	1.49
Lung . . . . .	0.5	0.26
Liver . . . . .	0.5	0.26
Kidney . . . . .	0.7	0.37
Bone (all long bones being analyzed) . . . . .	1.0	0.53
Total amount recovered . . . . .	5.5	2.91

As 2.8 mg. of germanium dioxide were recovered from 19 gm. of blood, which is about 30 per cent of the total blood content of an animal weighing 550 gm., the weight of the guinea-pig just prior to bleeding, it might be assumed that there existed in the total blood stream 14.7 mg. Moreover, it is noticeable by comparing Table VII and Table VIII that the removal of part of the blood gave a lower germanium content for the organs.

Hence, it may be assumed that the cumulative effect of germanium dioxide is negligible and that the blood stream carries as much as 0.014 per cent of germanium dioxide, this amounting to 10.49 per cent of the total dose in the entire blood stream.

**Elimination of Germanium Dioxide from the System.** A study of the elimination of the germanium dioxide was made upon a male rabbit weighing 2300 gm. During this period the animal was kept in a rubber-lined nutrition cage (precaution being taken to render the condition such that the samples would not come in contact with any metal). This rabbit received one large dose of germanium dioxide (234.2 mg.) intraperitoneally given in 50 cc of aqueous solution, following which dose a careful study was made of material eliminated. During the observation period of thirteen days the total urine and fecal material were collected at intervals indicated in Table IX.

Chemical analysis was made of these samples by the method as outlined previously in this article. The results of such analysis are tabulated in Table IX.

The preceding results show:

(a) The overdose of germanium dioxide is rapidly eliminated from the system, amounting to 139.7 mg., which is about 59.6 per cent of the total dose received. This occurred within a period of twenty-four hours following the dose, and analysis showed it to be practically entirely eliminated through the kidneys.

TABLE IX.—SHOWING ELIMINATION OF GERMANIUM DIOXIDE FROM THE SYSTEM OF A RABBIT. INTRAPERITONEAL INJECTION OF GERMANIUM DIOXIDE GIVEN DECEMBER 13, 1921. DOSAGE, 234.2 MG (50 CC OF SOLUTION).

Date of collection of samples.	Analysis of urine samples for germanium dioxide.		Analysis of fecal material for germanium dioxide.			
	Amount recovered in milligrams.	Percentage of original dosage.	Amount recovered in milligrams.	Percentage of original dosage.		
Dec. 14, 1921	132.7	56.66	7.0	2.98		
Dec. 15, 1921	2.7	1.15	26.2	11.19		
Dec. 16, 1921	3.7	1.58				
Dec. 17, 1921	2.1	0.90				
Dec. 18, 1921	2.4	1.03	5.0	2.13		
Dec. 19, 1921						
Dec. 20, 1921	1.9	0.81	6.4	2.73		
Dec. 21, 1921						
Dec. 22, 1921	1.2	0.51				
Dec. 23, 1921						
Dec. 24, 1921	0.3	0.13				
Dec. 25, 1921						
Dec. 26, 1921						
Dec. 27, 1921						
Total elimination	147.0 mg.	62.77	44.6 mg.	19.03		

(b) After the expulsion of the overdose the elimination becomes fairly constant over a long period and the amount eliminated from the intestinal tract increases slightly.

(c) From the results obtained about 81.8 per cent of the total dosage was accounted for within two weeks' time. This result in a measure explains the reason for the return of the erythrocyte curve to a constant in two weeks following dosage, which fact was pointed out previously in this paper.

A study was also made to determine the elimination of germanium dioxide from the system of man through the agency of the kidneys, analysis of the urine being made at definite intervals following a dose of 35.6 mg. germanium dioxide taken in 76 cc of aqueous solution through the mouth.

Table X shows the result of such a study:

TABLE X.—SHOWING ELIMINATION OF GERMANIUM DIOXIDE FROM THE SYSTEM OF A HUMAN BEING. DOSE TAKEN INTERNALLY (SOLUTION SWALLOWED) DECEMBER 11, 1921, DOSAGE 356 MG. (76 CC OF SOLUTION).

Date of collection of samples.	Volume of urine collected. cc.	Analysis of urine sample for recovery of germanium dioxide.	
		Amount recovered in milligrams.	Percentage of original dosage
Dec. 11, 10 A.M. to Dec. 14, 10 A.M.	2140	207.0	58.14
Dec. 14, 10 A.M. to Dec. 16, 10 A.M.	1780	6.5	1.82
Dec. 16, 10 A.M. to Dec. 17, 10 A.M.	750	2.3	0.64
Total elimination	4670	215.8	60.60

The results of this study show (a) that a dose taken through the mouth is absorbed into the system giving the same type of elimination as a dose given intraperitoneally into the system of the rabbit, and (b) the expulsion of the overdose is almost identical with that exhibited in the case of the rabbit.

**Conclusions.** The authors of this paper as a result of the present investigations conclude that:

1. Germanium dioxide has a decided erythropoietic action in the guinea-pig, rabbit, dog and man.

2. This erythropoietic action exerts a certain periodicity as shown in all of the erythrocyte curves obtained.

3. Relatively large doses of germanium dioxide are distinctly toxic, and from the results obtained it can be roughly calculated that the lethal dose is about 586 mg. of germanium dioxide per kilo of body weight.

4. This toxic action is not explainable on the basis of the accumulation of the compound in the system but is possibly due to an overstimulation of the blood-forming organs.

5. The quantitative method as devised by the authors for the determination of germanium dioxide in animal tissues and excreta, both in the presence and absence of arsenic, is an accurate method.

6. Germanium dioxide does not accumulate but is eliminated through the kidneys and alimentary tract. The overdose being rapidly eliminated and occurring chiefly through the agency of the kidneys, elimination by way of the alimentary tract is small.

The authors wish to express their appreciation of the kindnesses extended to them by Drs. A. C. Abbott, D. H. Bergey and H. F. Smyth during the course of this work, and to thank them also for the many valuable suggestions received.

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#### **LATENT NEUROSYPHILIS IN EIGHT PER CENT OF MEDICAL PATIENTS IGNORED OWING TO NEGLECT OF LUMBAR PUNCTURE.**

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How impossible it is for any group of specialists to "annex syphilology as a perquisite" has recently been remarked by a specialist in this field—Stokes, in 1920. An internist may therefore be permitted to oppose those who even today talk of "syphilomania" (Gandolfo in 1919) and "Wassermania" (De Meritt in 1920). The latter, for example, expresses the views of not a few "practical men" when he says, "I use this rather slangy term, the best I can invent, for a new and hitherto unnamed psychosis. . . . the

delusion that the health, the happiness and in fact the whole existence of syphilitic patients hang entirely on the results of frequent Wassermann tests."

Opposed to the above reactionary view we may group the demands for greater diffusion of our knowledge of syphilis, such as those by Cortlett in 1914, Collins in 1915, Irvine in 1916, White in 1917, Hazen in 1917, and most graphically perhaps by Pautrier in 1918, who wrote: "The ignorance of 95 per cent of doctors in dermatovenereology exceeds imagination. . . . It is truly scandalous. . . . The responsibility may be traced to a fearful gap in our medical teaching." This is startling testimony from a member of that nation which is currently believed to be particularly well-informed on this subject, a nation which has produced Alfred Fournier and his son Edmond Fournier. The former has more than once been called the first syphilographer of his time, and probably of all time; while with his son he is said, even by Dr. Leon Daudet in his extraordinary book of caustic comment on the best-known names in French medicine since 1880, to "have given to humanity out of an experience of forty years solutions to three-quarters of the problems of humanity."

Pleas, too, for more careful search in syphilitics for involvement of the cerebrospinal axis are nothing new. This is particularly true of lumbar puncture, but at the same time considerable conservatism is conspicuous in the recommendations as to the frequency with which it should be employed. These views progressively require puncture:

1. Only in proved syphilitics with frank neurological signs.
2. In patients with no nerve signs, but with mental symptoms.
3. In patients with neither nerve signs nor symptoms but only a suggestive history, such as of ptosis.
4. As a routine on every person known to have become infected with syphilis even though he has never shown symptoms.
5. The most advanced view of puncturing, despite denial of infection and despite a negative blood Wassermann, any individual reporting suggestive ills in a spouse, miscarriages, headaches, transitory lid-drop or any other unexplained nervous or mental symptoms.

The earliest downright demand for invariable lumbar puncture, and the one which stimulated the observations here reported, was that by Solomon in 1916. He agreed with Craig in 1915 in considering a positive Wassermann reaction as a symptom of syphilis; and recently, in 1920, in a most interesting paper, he gave further evidence of the reliability of the Wassermann reaction in competent hands, as illustrated by the remarkably parallel results reported on duplicates sent to the Boston City Department of Health (Dr. P. Castleman, director) and the Massachusetts State Department of Health (Dr. W. A. Hinton, director). From these standpoints he

went on to maintain the thesis that: "Syphilis may be considered a disease of remissions and exacerbations, the latent period merely a remission, following which a severe lesion is to be expected. Therefore when we treat a patient having a positive Wassermann reaction during the period of latency we are not treating the reaction but rather the patient for the purpose of curing him of a chronic disease and thus preventing a flare-up." From this he went on to contend that "in every case showing a positive Wassermann reaction a lumbar puncture is indicated for the purpose of examining the spinal fluid." Together with the late Professor Southard he returned to the charge in 1917, asserting that evidence is seldom searched for until neuropsychiatric symptoms or signs have appeared, and even then is regrettably rarely recognized.

**Personal Experience.** This advanced attitude stimulated a desire to detect neglected syphilis, and especially neurosyphilis, in such general medical patients as passed through our hands at the U. S. Army Base Hospital 76 at Vichy, Allier, France. The necessary intensive examination could, owing to lack of time, be applied to only a limited number of patients—namely, those on a special nephritic ward. During the first month, November, 1918, there were admitted to this ward thirty-one renal cases. The kidney conditions in these men have been reported elsewhere. Not one had a syphilitic register or clinical signs strikingly syphilitic. With the incidental constant desire to exclude syphilis, however, Wassermann reactions were done on the blood of each patient and positive diagnosis then was made in four men, *i. e.*, 13 per cent; and in three of these lumbar puncture gave evidence of involvement of the central nervous system, namely, in 75 per cent of the syphilitics or in 10 per cent of the medical cases. Simultaneously, among the same number of consecutive patients in the adjoining ward, under treatment for bronchitis or so-called "influenza," again all without known syphilis, the disease was detected in four (history of chancre, strongly positive Wassermann reaction, and in 1 case a tertiary skin blotch at the elbow), and of these 2 had negative spinal fluids and 2 had pleolymphocytosis, with strongly positive Wassermann reaction on the fluid. Protocols of the latter four patients are not at hand, but for the first four mentioned are abridged below, omitting the tests relating to the cardiorenal system, which were reported in the previous article.

In sum, then, among 62 patients with medical complaints not pointing to syphilis were 8 cases with that disease unrecognized, *i. e.*, 13 per cent of the total; and in 5 among these 8 (*i. e.*, 63 per cent of the syphilitics) the organ most gravely affected was the central nervous system. These figures while striking are not statistically significant, owing to the small number of patients. They agree, however, with those reported by others. First, relating to the frequency of unsuspected syphilis among miscellaneous medical

cases not previously supposed to be infected, but detected by routine Wassermann reaction, my 13 per cent falls between the 12 per cent reported by Walker and Haller in 1916 and the 17 per cent found by McLester in 1918. In the second place, as to the frequency of latent neurosyphilis in patients with positive bloods but hitherto supposedly normal central nervous system, Walker and Haller got 59 per cent, Corbus in 1917 got 30 per cent, Stokes and Brehmer in 1920 got 64 per cent, against the 63 per cent here reported.

Diagnosis of neurosyphilis was made after consideration of (a) the history, (b) the physical examination of the pupillary and patellar reflexes, coördination of finger-to-finger motions and of station (Romberg), (c) cells and complement-fixation in the spinal fluid. Such of these observations as were remarkable are recited in the protocols, and, as will there be seen, positive clinical findings were scarce, justifying, we believe, the consideration of these cases as belonging to the large group variously called unsuspected, cryptic, latent, ignored, asymptomatic, monosymptomatic or oligosymptomatic syphilis. The positive findings may be summarized. The history in the 4 case reports showed that 2 of the men (Rh. and Co.) had had treatment prior to service but none in the army, and that 2 (Le. and Rh.) had suggestive mental symptoms. Physical examination showed no skin or mucous membrane lesions; no general glandular enlargement; no heart or aortic disease; no eye-ground changes; no pathognomonic reflexes (especially note the normal pupils in patient Le.), though some slight abnormalities.

**Apprehensions and Answers.** Some may hesitate because of the possibility that the release of the cerebrospinal fluid may increase the permeability of the meninges for organisms circulating in the blood, as discussed for acute meningitides by Netter in 1887, 1909, 1911, 1915, Sicard in 1900, Achard and Laubry in 1902, Voisin in 1903, 1904, Sladen in 1910, Hutinel in 1912, Herrick in 1918, Weed, Wegeforth, Ayer and Felton in 1919, and especially exhaustively by Wegeforth and Latham in 1919. In answer it may be said: (a) That those observations related to acute meningococcus or pneumococcus septicemias, which are ordinarily excluded in chronic syphilis by the absence of fever and of other signs; (b) that so far little evidence is available to indicate that in syphilis the same process is to be feared; and (c) that even if such permeation to the spinal fluid be feared one can act safely by postponing lumbar puncture until the blood has been sterilized by intravenous injections of arsphenamin.

To those who hesitate because of the fear of causing headache, one may point out that this is practically always preventable by lying flat in bed for forty-eight hours, thus allowing the hole in the dura a chance to heal and stop the "occult leakage" and consequent lack of support to the brain, which was surmised to be the cause by Sicard, as cited by Widal in 1901 and confirmed by MacRobert in 1918 and by Wegeforth and Latham in 1919.



To those who hesitate because of the evidence that the cerebrospinal fluid may be abnormal only transiently, one may point out the words of Collins in 1920 on "Syphilitic Scars of the Spirit:" "The chief object in calling attention to this variety of cerebral syphilis is to emphasize the fact that although the infection is thwarted and the patient regains what seems to be his health, he is left with a scar of his mind. . . . The lesson is that the earlier the treatment is instituted the greater the chance of functional recovery."

**Position of the Patient for Lumbar Puncture.** On the suggestion of Dr. A. B. Brower, of Dayton, Ohio, the Sam Browne belt with sling removed was used instead of the knotted sheet placed by some around the neck to hold the chin against the knees, to keep the lumbar spine well arched and immobile and to afford the patient something firm to strain against. Out of twenty punctures only one patient made a "fuss" at the idea of the harness, and he finally consented to put it on himself. A plank was put under the mattress along the edge of the bed to prevent sagging and consequent lordosis of the patient, who lay on his left side. Besides this method of securing the good position so advantageous for insertion of the needle through muscular backs, morphin, 0.015 gm. s.c., was also administered to many of the patients.

**Protocols.** CASE III.—Gr., aged thirty-three years; laborer; private of infantry; service of ten months; measles in 1890; typhoid in 1909; venereal disease denied by name and symptoms, including rash, sore mouth and other secondaries, but exposures from 1902 to 1918.

*Present Illness.* Nocturia since October 26, 1918; dyspnea since October 26 on exertion only; edema of feet and face, marked from October 26 to November 8, only slight since; seen November 12, 1918 to January 11, 1919.

*Examination.* Reflexes: Pupils equal; irregular; react poorly; KJ normal; Romberg normal; serum Wassermann reaction strongly positive; cerebrospinal fluid cells 0; Wassermann reaction negative.

*Diagnosis:* (1) Syphilis; (2) nephritis, acute, October 26, due to exposure, severe; (3) hypertension.

*After-history:* Follow-up letter in March, 1921, not answered.

CASE X.—Le., aged thirty-two years; piano teacher; private of engineers; service of seventeen months; venereal exposure denied but probably acquired from wife; married in June, 1917, separated in three months because she gadded about and went often to a doctor, but would not tell why (cf. case reported by Gookin in 1919).

*Present Illness.* Headache since fall of 1917, (?) due to syphilitic meningitis; sensitive to cold since May, 1918; loss of memory since July 20, 1918; previously played concertos from memory; nocturia

since September 20, 1918; dyspnea since October 3, 1918; (?) due to syphilitic myocarditis; November 1, 1918, mental concentration impaired; November 9, incontinence.

*Physical Examination.* Eyelids puffy; pupils equal; circular and react well to light; KJ equal but hyperactive; no Romberg; no hand ataxia; hyperactive rectus and cremasteric reflexes; the only palpable glands are two in the left axilla. Serum Wassermann reaction strongly positive; cerebrospinal fluid and Wassermann reaction strongly positive, cells 46. Seen from November 19, 1918, to January 19, 1919.

*Diagnosis:* (1) Neurosyphilis; (2) nephritis, acute; onset September 20, 1918, due to exposure or possibly to syphilis, apparently in early stage of nephritis.

*After-history:* Letter in March, 1921, not answered.

CASE XXVI.—Rh., aged twenty-nine years; pay-roll clerk; private in field artillery; service fourteen and a half months; measles at six; mumps at seven; typhoid in 1912; gonococcus urethritis in 1916, treated for one month; also in 1916 both soft and hard chancres treated with injections into the paravertebral muscles of six ampules of (?); no mercury iodide or arsenic so far as he knows; no secondaries. Scabies for two months in 1916 and from October 1 to December 31, 1918. Concussion by burial up to the waist in a collapsed dug-out October 10, 1918; mild; cured October 10; sprain of right knee by that burial; cured October 26; abrasion of the right knee from falling timber in same dug-out October 8; cured November 18; influenza November 20 to 25, 1918; exposure to weather for the past two months; habits, alcohol in excess.

*Present Illness.* Nocturia since November, 1917; sleep restless since July 1918, *i. e.*, for five months; "lightheaded" in October and November, 1918; numbness in the lower legs for a month; no lancinating pains or crises.

*Examination.* Pupils equal but irregular and react poorly, KJ normal; Ach. J. equal but hyperactive. Romberg: slight; hand ataxia slight; serum Wassermann reaction strongly positive; cerebrospinal fluid Wassermann reaction strongly positive; cells 210. Seen December 5, 1918, to January 19, 1919.

*Diagnosis:* (1) Neurosyphilis, onset 1916; (2) nephritis, chronic, onset in November, 1917, apparently due to exposure.

*After-history:* Letter in March, 1921, not answered.

CASE XXXI.—Co., aged twenty-seven years; carpenter; private of infantry; service five and a half months; diphtheria; mumps and scarlet fever at about three; chicken-pox, measles and pneumonia at four years; scabies in 1904, typhoid in 1908, chancre in 1911, treated by 75 pills (? Hg), no KI or 606. Gonococcus urethritis in 1917 for three weeks; diarrhea September 6 to December 4, 1918;

exposure to weather for the last two months; eats considerably more meat and salt than the average.

*Present Illness.* G. S. W. right thigh. Seen December 10, 1918, to January 19, 1919.

*Examination.* Pupils equal, irregular and react poorly; KJ equal but rather hyperactive; Romberg slight. Glands: ax. and ing. slight; spleen 3 cm. below C.M., serum Wassermann reaction strongly positive, and cerebrospinal fluid Wassermann reaction strongly positive; cells 25.

*Diagnosis.* (1) Syphilis, onset 1911; (2) neurosyphilis, onset ?; (3) splenomegaly, onset ?; (4) nephritis, acute, onset December, 1918, apparently due to diarrheal infection.

*After-history:* In March, 1921, wife reports patient dead, cause unknown.

**Summary.** 1. In 62 medical cases, all supposedly non-venereal, were found 8 syphilitics, only 2 of whom knew of their disease.

2. In these 8 syphilitics were 5 with C. N. S. involvement, hitherto unrecognized in all.

3. The army principle of relying on the physical examination and neglecting the history leads to the overlooking of syphilis in the army.

4. Since neurosyphilis is so important it should be more generally suspected in an internal medical clinic.

5. Lumbar puncture should be done (preferably after preliminary fundus examination) on every syphilitic. If positive it should be repeated rather frequently, at least annually, until it has been negative for one year; and thereafter every two years, to exclude recurrence. This, though drastic, is milder than tabes or G. P. I. Watchful waiting in syphilis does far more harm than occasional accidents incident to puncture.

6. The Sam Browne belt was a useful adjunct.

I am indebted to former associates in Base Hospital 76, especially Dr. I. I. Lemann; of New Orleans, Dr. A. B. Brower, of Dayton, Ohio, and Mr. E. E. Wagner, of Newport News.

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## ROENTGEN-RAY STIMULATION OF THE PANCREAS IN EXPERIMENTAL PANCREATIC DEFICIENCY.

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In a preliminary communication<sup>1</sup> we have called attention to the fact that with roentgen stimulation of organs two distinct methods of approach may be considered, the one direct and the other indirect. The first would include the stimulation of dys- or hypofunctioning organs with the purpose of restoring function to the normal plane. The treatment of anuria in acute parenchymatous nephritis; hepatic intoxication in some forms of cirrhosis; achylia; anemia of certain types; particularly endocrine disturbances—the ovaries in some forms of amenorrhea, the testicles (as in Steinach experiments), the hypophysis in growth disturbances, the adrenals in Addison's disease, the pancreas in diabetes—are but a few illustrations of the possibilities of this first method.

<sup>1</sup> Petersen, W. F., and Sælhof, C. C.: *Jour. Am. Med. Assn.*, 1921, 76, 718.

The second, or indirect method, includes the stimulation of normal organs and the augmentation of serum enzymes, thromboplastic substances, antibodies and so forth, and therewith bringing about therapeutic effects on systemic or localized infections, or other pathological processes. We have previously called attention to the possibility of using roentgen stimulation of organs to mobilize enzymes<sup>2</sup> in this manner. Since our work was completed, Kaznelson and St. Lorant<sup>3</sup> have published experiments similar in character, but dealing with other serum alterations—fibrinogen, blood sugar, bilirubin, catalase, antibodies—which confirm our results. Kaznelson and St. Lorant discuss the possibility that roentgen-rays may act as non-specific agents (plasma-activation) and describe a series of focal reactions after roentgen-ray treatments similar to those that can be elicited with other non-specific agents.<sup>4</sup>

In view of the admitted limitations in the treatment of diabetes we have investigated the possible effect which roentgen stimulation of the pancreas might have on the carbohydrate tolerance of partially depancreatized dogs, and present a number of representative protocols and charts to illustrate the effects which we have observed.

**Experimental.** One of our first experiments was made on a dog in which an almost complete pancreatectomy had been carried out (with only very small portions of glandular tissue left). After recovering from the operation the animal was placed on a constant diet of 100 gm. of protein and 50 gm. of carbohydrate (dried cracker meal). The daily volume of urine, the sugar excretion and the acidosis are recorded in Table I.

TABLE I.

Dog 18.	Volume.	Gm. dextrose.	Diacetic acid.	Acetone.	Blood sugar, mg. per 100 cc.
Oct. 28 . .	490	40.6	x	x	
29 . .	275	27.7	x	x	
30 . .	300	13.5	x	x	
31 . .					
Nov. 1 . .	175	10.9	x-	x-	
2 . .	420	34.0	x	x	
3 . .	350	43.0	..	..	.. X-ray for ten minutes:
					Before x-ray . . . 8.0
					1 hr. after x-ray . . 8.9
					5 hrs. after x-ray . . 6.4
4 . .	280	26.8	x	..	
5 . .					
6 . .	450	{ 17.0	..	..	
		{ 17.0	..	..	
7 . .	350	39.0	..	..	

<sup>2</sup> Petersen, W. F., and Sælhof, C. C.: AM. JOUR. MED. SC., (In print.)

<sup>3</sup> Allgemeine Leistungs-steigerung als Fernwirkung therapeutischer Roentgen bestrahlung, München. med. Wehnschr., 1921, 68, 132.

<sup>4</sup> Petersen, W. F.: Focal Reactions, Am. Rev. Tuberc., 1921, 5, 218.

It will be observed that the sugar excretion increased for the day of the roentgen exposure (to 43 gm.), then diminished for three days, and with the fourth day had again reached the previous level. Some evidence of a reduction in acidosis is apparent in the fact that after the irradiation both acetone and diacetic acid disappeared from the urine. The roentgen exposure was for ten minutes, six-inch spark, (Coolidge tube) screen 3 mm. aluminum, 5 ma. and 10-inch focal distance. The area exposed consisted of the anterior upper abdomen. In view of the fact that very little pancreatic tissue had been left in the animal we cannot expect much evidence of increased carbohydrate tolerance, but the excretion sequence 34, 43, 26, 17, 17, 39 would indicate first an augmentation of excretion, followed by some increase in carbohydrate tolerance.

In the dog used in the following experiment approximately 1 gm. of pancreatic tissue was left *in situ* along the gastroduodenal attachment. The animal weighed 7 kilos, was operated on October 1 and was placed on a constant diet, 100 gm. of protein and 50 gm. of carbohydrate (cracker meal) as soon as recovery had taken place. The average dextrose elimination for the week ending October 8 was 20 gm.

In Table II the effect of roentgen stimulation (dose as before) is shown:

TABLE II.

Dog 20. Date Oct.	Volume. cc.	Dextrose.		Diacetic acid.	Acetone.	Blood sugar, mg. per 100 cc.
		In per cent. (Average for week)	In gms. 20.0			
	8			x	x	5.21
Rayed	Oct. 9 350	5.5	18.7	x	x	5.21
	10 620	5.5	34.1	x	x	6.54
	11 490	5.0	24.5	x	x	6.54
	12 320	0	0	x	x	6.18
Rayed	13 510	0	0	x	x	2.58
	14 560	3.3	18.5	tr.	..	1 hr. after x-ray . 2.58
						5 hrs. after x-ray . 2.0
	15 650	.3	1.9			
	16 370	2.0	7.4			
	17 225	2.2	4.9	tr.		
	18 400	3.3	13.2	x	x	
	19 360	4.5	16.2	x	x	
	20 270	7.15	19.3	x	x	
	21 225	10.0	22.5	x	x	
	22 150	12.75	18.75	x	x	Before x-ray . 1.92
	23 170	7.10	12.0	tr.	x	1 hr. after x-ray . 2.08
						5 hrs. after x-ray . 1.9
	24 140	8.34	11.67	x	x	
Rayed	25 130	6.25	8.12	..	..	
	26 440	9.18	40.4	..	..	
	27 100	10.0	10.0	..	tr.	
	28 450	7.1	32.0	x	x	

It will be observed that after the preliminary increase in sugar excretion, complete tolerance was established three days after the first irradiation. A second exposure at this time resulted in a typical rise in sugar excretion, this time to be followed by a tolerance not quite as good as before. The third treatment again resulted in some effect on the sugar tolerance as well as an effect on the acidosis.

In the next experiment (Chart I) a partially pancreatectomized dog (No. 43) was kept on the constant diet of 100 gm. of protein and 50 gm. of carbohydrate except for one day, when an additional 150 gm. of dextrose were added to the feeding (second day on chart). This animal was given two roentgen exposures over the pancreatic area, one of ten minutes' duration in the morning of the 6th and one in the afternoon of the same day. In this animal there was no evidence of the usual increase in the amount of sugar excretion that we frequently find for the first twenty-four or sometimes forty-eight hours after the irradiation, but a definite diminution in the amount of dextrose eliminated, despite the fact that there was an increase in the amount of blood sugar.

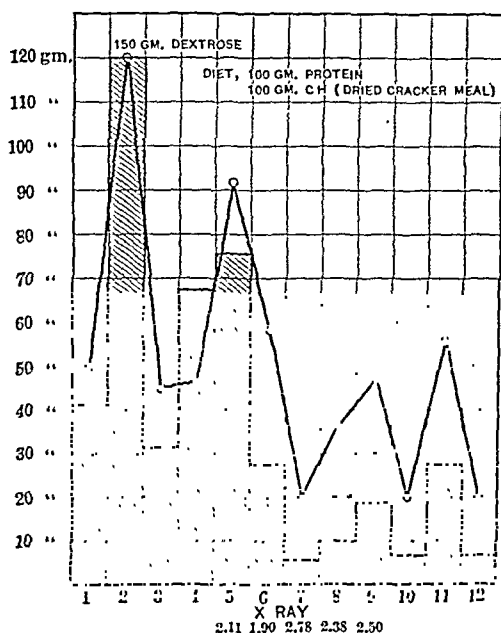


CHART I.—Effect of irradiation on sugar excretion. Rayed on the 6th. Shaded columns = gm. dextrose excreted per day. Curve = volume of urine per day.

In the following experiment (Chart II) evidence is presented (a) that the mere increase in sugar elimination, such as is often observed for a day or two after irradiation, does not bring about an increased tolerance when induced by general protoplasmic stimulation (turpentine abscess) and (b) that irradiation of areas other than those containing the pancreatic rest does not increase the carbohydrate tolerance. The animal was partially pancreatectomized on December 1, and after the tolerance had been determined the animal was placed on a constant diet, 100 gm. of protein and 50 gm. of

carbohydrate and bone ash on December 26. On January 5 three cutaneous injections of turpentine in olive oil (1 cc of 20 per cent turpentine in oil) were made to produce small sterile abscesses. The effect on the sugar excretion is at once apparent in the large amount excreted, but despite the increase no final increase in tolerance resulted.

On the afternoon January 12 and the morning of the 13th the animal was rayed over the pancreatic area for ten minutes. The effect on the sugar excretion was typical—first an augmentation, then a reduction on the third day after irradiation to 0. It will be observed that this was the only time during the course of the experiment that the animal was sugar-free for twenty-four hours.

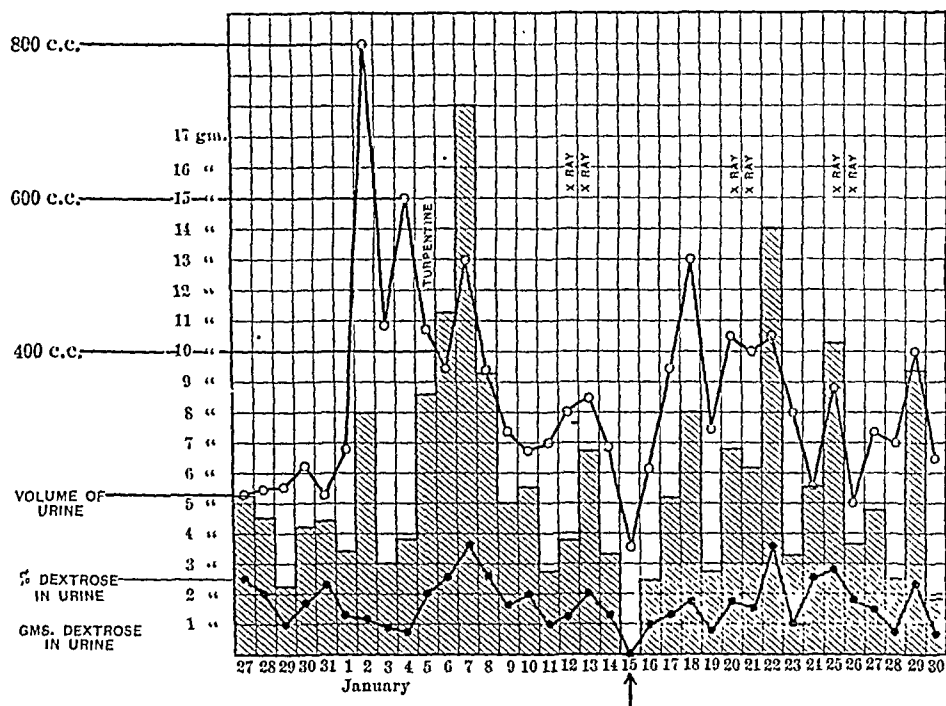


CHART II.—Effect of Roentgen-ray stimulation of pancreas on sugar excretion.

On the afternoon of January 20 and the morning of the 21st the animal was again rayed, this time over the liver area. While the usual increase in sugar excretion was apparent there was no reduction in the amount of sugar excreted. On January 25 and 26 the lower abdomen was rayed; in this case there was little increase in sugar output.

The following experiment (Chart III) illustrates the fact that the effect of irradiation of the pancreas does not produce merely a transient increase in carbohydrate tolerance, but one that may persist for some time after the exposure, in this particular experiment for at least eight days.



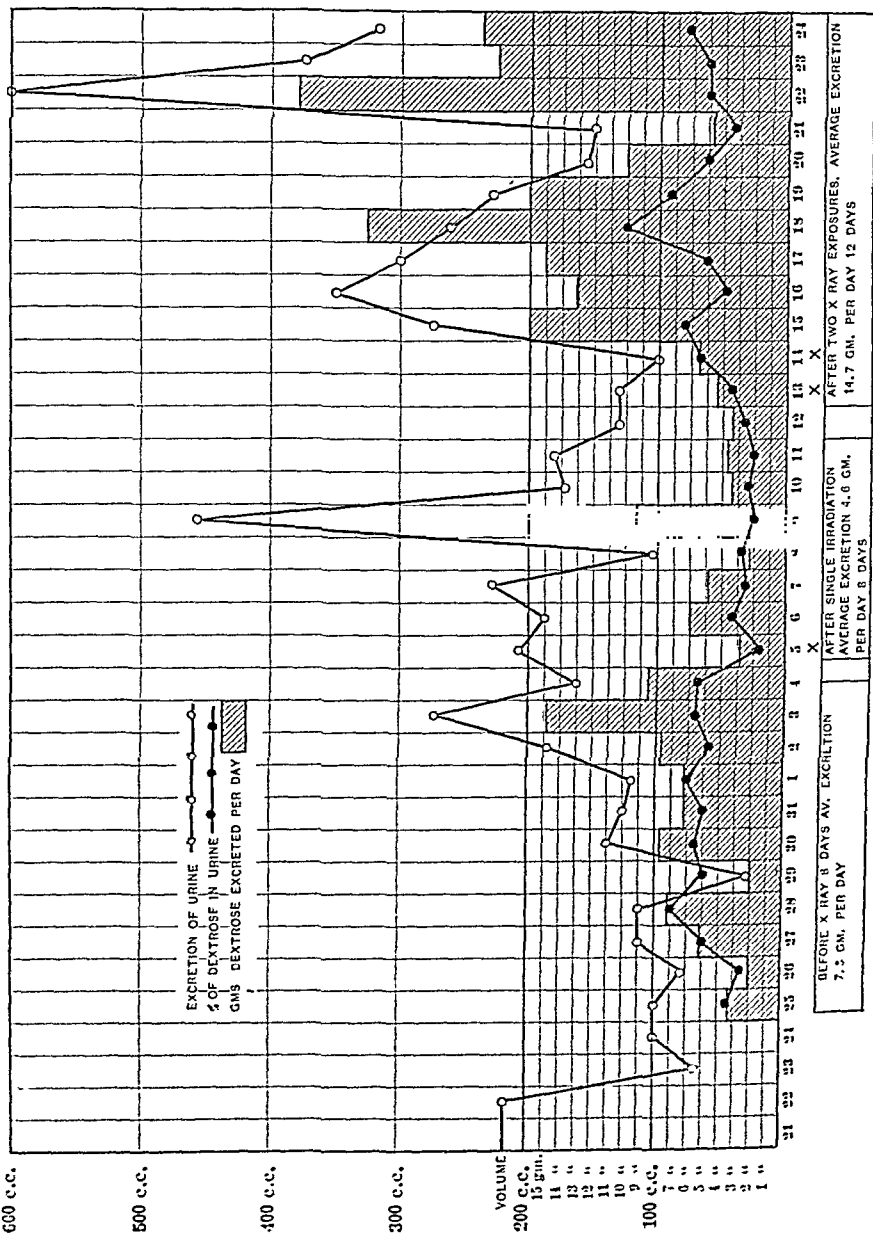


CHART III.—Effect of stimulating and depressing dose of Roentgen-rays on sugar tolerance.

At the time of the operation (March 21) the animal weighed 5 kilos (Dog No. 44) and 7 gm. of pancreatic tissue were removed. On March 27 the animal was placed on a constant diet (100 gm. of meat and 50 gm. of dried cracker meal). No acetone or diacetic acid were present at any time.

It will be observed that the average dextrose elimination for the period of eight days previous to the first roentgen exposure was 7.3 gm. per day. Following the single irradiation the excretion fell at once (without the usual transient rise) and averaged 4.6 gm. for the following period of eight days. At the end of this time the animal was again exposed, the dose being doubled (two periods of ten minutes each two days in succession). It is at once apparent that in place of stimulation the dose was sufficiently large to cause depression of function (destruction) and the carbohydrate tolerance sinks, with a daily excretion averaging 14.7 gm. per day. The animal weighed 4.5 kilos at the end of the experiment.

**Discussion.** Efforts made to influence carbohydrate tolerance by means of irradiation have taken several courses. When the diabetic patient is treated with radium emanations the general metabolism may be stimulated, and, as a rule, more dextrose is eliminated than before the treatment.<sup>5</sup> The same observation holds true for roentgen exposure when deep therapy is attempted in diabetic patients who come under treatment for various unrelated pathological conditions (tumors, furunculosis, neuritis, etc.).

Solomon<sup>6</sup> has endeavored to alter the carbohydrate metabolism by roentgen treatment of the liver. This has not been successful in the diabetic; indeed, stimulation of the liver parenchyma is practically always followed by an increase in sugar excretion. Roentgen stimulation of the liver alters the titer of the serum diastases, but we find no effect on the diabetes as a result; the sugar excretion seems quite independent of the titer of these enzymes.

Another line of approach to the problem has been that pursued by Dresel,<sup>7</sup> who has sought to alter the function of the pancreas by depressing the activity of the adrenals by roentgen exposure. He has obtained thereby a transient effect on the carbohydrate tolerance. Dresel's experiments offer a striking example of the tendency one finds so often in roentgentherapy, namely, the constant effort to use roentgen and radium rays as destructive agents rather than their employment in their more proper and more useful sphere as stimulating agents.

In a review of the literature of the subject we find but one paper

<sup>5</sup> Falta, W.: *Die Behandlung innerer Krankheiten mit Radioaktiven Substanzen*, Berlin, 1918.

<sup>6</sup> Quoted by Stephan.

<sup>7</sup> Ueber Herabsetzung des Blut- und Harnzuckers durch Roentgenbehandlung der Nebennieren beim Diabetiker, *Deutsch. med. Wchnschr.*, 1920, 46, 1240.

which deals with the possible direct stimulation of the pancreas by means of irradiation. Stephan<sup>8</sup> has reported two cases of severe diabetes in which he was able to influence the carbohydrate tolerance favorably by means of deep roentgentherapy over the pancreatic area.

Inasmuch as Stephan's paper may not be generally available we present his results in Tables III and IV.

The first patient was twenty-four years of age, with a severe diabetes that did not show improvement under strict dietary control.

The output of urine and of dextrose was as follows (the diet being constant, 100 gm. bread plus proteins and fats to make up a total caloric value of 2400):

TABLE III.—EFFECT OF IRRADIATION ON DIABETIC PATIENT.  
(STEPHAN.)

7	4200 cc	159.	Roentgen-ray treatment. (Furstenau-Coolidge tube, 160,000 volts; 22 ma; focal distance 22.5 cm.; 25 minutes (erythema dose, 35 m.), with screen of 0.5 mm. zinc and 3 mm. aluminum.)
8	4600 cc	207.	
9	3800 cc	171.	
10	3800 cc	190.	
11	3700 cc	166.	
12	3900 cc	175.	
13	4550 cc	172.	
14	3100 cc	102.	
15	3600 cc	109.	
16	3650 cc	127.	
17	3550 cc	119.	
18	3000 cc	183.	
19	2600 cc	140.	
20	2800 cc	104.	
21	2700 cc	95.	
22	2850 cc	91.	
23	3300 cc	137.	
24	4500 cc	199.	
25	3400 cc	183.	Rayed for twenty minutes.
26	2850 cc	144.	
27	3650 cc	153.	
28	3100 cc	117.	
29	3600 cc	153.	
30	3750 cc	148.	
1	3500 cc	127.	
2	3150 cc	115.	

Acetone and diacetic acid were present at all times before and after treatment. It will be observed that after the first exposure there was a well-defined but transient effect on the sugar output while the second irradiation was without effect. Clinically the patient was improved, particularly the subjective discomforts were less severe.

The second case was a man, aged thirty-two years, on a similar diet:

<sup>8</sup> Steigerung der Zellfunktion durch Roentgenstrahlen, *Strahlentherapie*, 1920, 11, 517.

TABLE IV.—EFFECT OF IRRADIATION ON DIABETIC PATIENT.  
(STEPHAN.)

March	11	4500	270.	
	12	5500	275.	
	13	3500	172.	
	14	4300	215.	
	15	4500	270.	
	16	4300	215.	(Roentgen ray (twenty five minutes).
	17	5600	252.	
	18	2400	134.	
	19	3700	185.	
	20	4000	232.	
	21	2900	145.	
	22	4100	164.	
	23	4700	216.	(Vegetable day.)
	24	1800	36.	
	25	3400	112.	
	26	3400	193.	(Oatmeal day).
	27	4500	184.	
	28	4000	228.	
	29	4050	243.	(Roentgen ray (twenty minutes).
	30	3050	137.	
	31	4900	245.	
April	1	4400	202.	
	2	3700	185.	(Vegetable day).
	3	2550	96.	
	4	4500	211.	
	5	4900	205.	(Potato day).
	6	5800	220.	
	7	3300	184.	
	8	2600	148.	

After this time the patient was under observation at various times, and it was observed that the tolerance had markedly increased two weeks after the second irradiation. Acetone and diacetic acid, which had been constantly present in the urine to the 25th of the month, disappeared thereafter (ten days after the first irradiation). Stephan believes that the stimulation by the roentgen ray is not only a transient one, but becomes more apparent several weeks after the treatment.

A number of interesting problems present themselves in connection with the results that follow irradiation of the pancreas. These concern the method of action, the duration of the effect, the proper dosage, the possible clinical application and the possibility of connective-tissue stimulation (fibrosis).

We are of the impression that the effect is simply an illustration of the old Arndt-Schulz observation that irritants which in large doses injure the cell will in small doses induce functional stimulation.<sup>9</sup> The experiment illustrated in Chart III shows this effect very clearly in that the dextrose elimination on a standard diet was reduced to 4.6 gm. per day from a normal 7.3 gm. after a stimu-

<sup>9</sup> Virchow had expressed this same idea many years before when he stated that "mild irritants bring about functional stimulation, stronger ones act on the nutritive activities, severe ones bring on formative (reproductive) alterations and the strongest irritants kill." Virchow's Arch., 1858, 14, 24.

lating dose over the pancreatic area, and when the roentgen dose was doubled (with cellular depression instead of stimulation) the sugar output increase to 14.7 gm. per day. We believe the effect is directly on the pancreatic tissue (and not merely to a hyperemia) because of the duration of the effect.

Concerning the duration of the effect we have as yet no conclusive data. In most of our animals the effect was relatively transient—four or five days—with a return of the pre-irradiation level. In the experiment shown in Chart III the effect was still apparent after eight days, and in one other animal the increased tolerance had persisted for a month. Stephan has gained the impression from his clinical cases that the effect is not only an immediate one of short duration, but one that is still apparent several weeks after the treatment.

The proper dosage in animals and in clinical cases will depend entirely on the apparatus available. When properly screened and the rays homogenized our relatively low voltage apparatus has no great penetration, so that we can expect little effect on the pancreas with any dose much under the full erythema dose. In animal experiments the conditions are more favorable in that the pancreatic tissue lies nearer the surface and the epidermis is much more resistant to irradiation.

While we would not at the present time suggest the clinical application of the method in the diabetic amenable to dietetic treatment until more exact knowledge is gained concerning the ultimate effect of roentgen stimulation on the pancreatic tissue, it might perhaps be warranted to make use of the method in conditions of diabetic coma when other methods of treatment have failed. But even in such conditions it should be kept in mind that the roentgen stimulation is at times first apparent in an augmentation of sugar output due to the general tissue stimulation of the abdominal viscera, an effect which we cannot absolutely control because it is in part an effect of secondary radiation.

**Summary.** From our experiments we have drawn the following conclusions: In experimental pancreatic deficiency due to partial pancreatectomy roentgen irradiation of the pancreatic rest may be followed by (a) a transient increase in sugar output, then by (b) an increase in carbohydrate tolerance. This later may occur without the preliminary increase in sugar excretion. The increased tolerance may be transient or may extend over a period of several weeks after irradiation. (c) The increased tolerance is not due to the preliminary increase in sugar elimination. When increased sugar elimination is brought about by some other irritant (turpentine abscesses) no increase in carbohydrate tolerance is later observed. (d) The effect on the blood sugar varies. Usually a temporary increase in the blood sugar can be determined, followed by a lowering of the level that takes place in from five hours to several days after the

irradiation. (e) When evidences of acidosis exist at the time of irradiation they may diminish or disappear with the improvement in the sugar tolerance. (f) The effect of irradiation on the pancreas is due to direct stimulation of cellular metabolic processes and not due solely to alterations primarily vascular. (g) This stimulation is merely an example of the Arndt-Schulz observation that cell irritants in small doses stimulate metabolic processes. (h) When the irradiation is used in too large a dose, injury to the pancreatic function is apparent in a diminution in carbohydrate tolerance. (i) When tissues other than those containing the pancreatic rest are irradiated no effect is observed on the carbohydrate tolerance other than the primary augmentation of sugar excretion. (j) The titer of the serum diastases, which may be altered by irradiation of the liver, seems to be without influence on the tolerance.

Blood sugar determinations were carried out by Dr. Kraft, to whom we are under obligations.

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## INFECTIOUS ARTHRITIS OF THE SPINE\*

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ARTHRITIS of the lumbar spine traceable to infections is a common cause of low back pain. The cases herein described are characterized mostly by their mildness, by their ability to walk, by the involvement of the vertebræ and the perivertebral tissues, by the presence of lateral deviation of the spine and by the absence of sharp, angular kyphoses. Two of the patients have been previously treated for sciatica by means of massage and electricity; epidural injections have been done without success. They all complained of pain in the sacro-iliac region, and with striking frequency, they were labeled sacro-iliac slipping. The course was self-limited and several months was the average time lost from disability.

It is intended to omit any reference to gonorrheal, syphilitic or tabetic spines, as well as those of infancy and childhood. All Wassermann tests were negative.

In P. W. Nathan's paper on "Polyarthritis and Spondylitis," published in 1916, after an account of a series of experimental streptococcemias in dogs, he states: "It therefore becomes necessary to classify the spondylitides according to the presence or absence of neural symptoms, the mode of progression or the involve-

\* Read before the Orthopedic Section of the New York Academy of Medicine, November 19, 1920.

ment of the ribs and joints of the extremities. Whether these structures are involved or not is simply an accident of localization and does not depend upon peculiarities or essential differences in the etiology or the pathogenesis of the morbid process. It is, then, no longer necessary to specify by name the type of the spondylitis (Bechterew, Strümpell, Pierre Marie, etc.); these conditions are not essentially different; they are all simple variations in the location of some inflammatory condition which, like all inflammatory conditions, may be acute or chronic, transient or progressive, with or without permanent damage to the tissues involved."

Traumatic surgery of the spine was an attractive field during the World War, and many articles have appeared in the literature of the spine and spinal cord. On the non-surgical affections of the spine that are so common in civil life there has evidently been less material to stimulate description. While on duty in army hospitals I saw many instances of infectious arthritis and peri-arthritis, but none affecting the spine. Traumatic and tuberculous cases seemed to form the greater part.

Lance and Jaubert, in the *Revue de chirurgie*, August, 1919, mention the frequency with which spondylitis and perispondylitis were encountered among French soldiers. Their service was in the hospitals in the Maritime Alps, to which patients were sent for heliotherapy, with the diagnosis of Pott's disease or the infectious arthritides of the spine complicating pulmonary tuberculosis. They describe eighteen cases, dividing themselves into two groups: (a) Four cases of spondylitis of infectious origin, definitely determined (that is, staphylococci, streptococci, Eberth's and paratyphoid bacilli), were found; (b) fourteen cases of perivertebral lesions in which the etiology is debatable and in which purely bone lesions do not appear except in a few instances. This group embraces many polyarticular cases with stiff spines, mostly with bow-backs—the von Bechterew type.

Case 1 was an army colonel, aged fifty-three years, whose thigh had been amputated two months before for staphylococcus infection; he later suffered from an ischiorectal abscess, also staphylococcal, following which he developed a painful gibbus. Roentgen ray disclosed destruction of the bodies of the eighth and ninth dorsal vertebrae, disappearance of the intervertebral disk, and fusion of the two bodies.

Case 2 of their series was a colonial soldier, aged twenty-eight years, in hospital for otitis purulenta, bronchitis, ophthalmia and abscess of the knee. Streptococci were recovered. Three weeks later he had symptoms of Pott's disease; he suffered from extreme sensitiveness and excruciating lumbar pain for five months. Roentgen ray then demonstrated diminution in height of the fourth and fifth lumbar, effacing of the intervertebral space and squashing of the right half of the body of the fourth lumbar. On the right

border of the two affected vertebræ are noted new periosteal formations (deposits) well marked, especially around the transverse processes, which were treated by means of the plaster corset.

Case 3, a soldier, aged thirty years, old otitis media purulenta, had typhoid fever in September, 1916; defervescing on October 20, when he developed a backache, rigidity of the back and paresis of the lower extremities. Coincident recurrence of the otitis. Lumbar puncture yielded clear fluid and gave momentary relief. In December, roentgen-ray showed a collapse of the second and third lumbar vertebræ, one upon the other. Plaster jacket applied. In February, rigidity of the entire column was noted, with pain on attempted movement. By October, 1917, the first lumbar intervertebral disk was half destroyed and the second and third bodies completely fused. There was some destruction of the second disk. The two vertebræ have the characteristic form of the toy "diabolo" (*i. e.*, reel-shaped or spool-shaped) of perispondylitis. The fifth lumbar appears collapsed and shortened, with the disk one-half destroyed and the other half ossified.

Case 4 was a farmer. After paratyphoid a positive blood culture was made February 3, 1915. In April, there was severe, sudden sacrolumbar pain, with fever. He was disabled for two months. A lateral lumbar deviation was noticed. In January, 1916, there was a small gibbus and total lumbar deviation. In March, the radiograph revealed collapsed and fused fourth lumbar, especially on the right half of each; the intervertebral disk between them has disappeared and a large mass of perivertebral ossification is seen at this level at the right and around the base of the spinous process. Two excrescences from ligamentous ossification were noted. He was discharged in May, 1916, decidedly improved.

The region of the back between the tenth dorsal level and the trochanters furnishes as much food for clinical study as the romantic area of the right upper quadrant of the abdomen. Heavy muscles cover the spine, rendering it difficult to palpate. These same muscles cause profound changes in symmetry of the entire trunk when their function is directly or indirectly impaired. The bony structures are complex in their arrangement and in close proximity to important nerve trunks, whose irritation, in the presence of joint disease, may have far-reaching effects. As a result of the obscurity of some of these lesions we behold queer diagnoses and questionable healing cults.

Pancoast<sup>1</sup> says: "Lumbar spines are easiest to view in antero-posterior plates. The bodies are so large in comparison with the other portions of these vertebræ, the shadows of which are less confusing than in the cervical and dorsal spine. The intervertebral spaces are wide, and with the transparent disks permit a fairly

<sup>1</sup> Frazier's Surgery of the Spine.



clear view of the laminae, which project downward between the bodies. Likewise the intervertebral joints are frequently on a level with the disks, and as the articular surfaces are nearly in an antero-posterior plane the entire joint line is usually visible. These joints can be more adequately studied in this region than elsewhere, and slight displacement and the lesions of chronic arthritis can frequently be detected."

Any lumbar deviation in a patient who suffered from pain along the course of his sciatic nerve has been called sciatic scoliosis. Homologous and heterologous are adjectives, referring to whether the patient turns from or toward the painful extremity. The muscles concerned in the distorting process are supposed to be the flexors of the hip and the lumbar muscles, especially the powerful quadrati. What interests us here is the presence of bone or joint affections in the spinal column in a large number of adults who have the same deformity and the same symptoms. Cases of low-back pain, in which a lateral centering of the spine occurs and in which careful radiography demonstrates lesions here described, *should not be classed under the caption of the idiopathic scolioses of adults.*

A definite list is due to osseous thickening and muscular spasm when we exclude evanescent cases of lumbago. It can be directly translated in terms of inflammatory exudates, adhesions, absorption of cartilages, destruction of bony tissue, deposits, excrescences and ankylosis. The process in acute severe cases is one of rapid softening of a vertebral lip, contraction or shortening of a meniscus, soon eventuating in a rounded lumbar kyphosis. Softening and destruction of one-half of the upper margin of the last lumbar will most readily produce lateral deviation of the trunk. These changes may occur before they are recognizable in a roentgen-ray plate. A kyphoscoliosis coming on in the short space of a few weeks appears to be much more of a complicated mechanical process. It can be explained by a massive softening, destruction involving the lateral articulating processes, following by a partial sliding of an entire vertebral body to one side. The usual phenomena of arthritis ankylogica follow and the organization of ligaments results in calcified bands of spondylitis deformans.

A distinct limp from psoas irritation disappeared in all the cases under observation for a sufficient length of time. A persisting contraction usually means a polyarthritis with hip involvement, which has been omitted in this communication.

The deformity has diminished under treatment, as is the rule in mild cases of spinal osteo-arthritis. The alignment returns unless the vertebrae have assumed a rotary lateral deformity, as in one of my cases. A small degree of bony adhesion, say between two or three vertebrae, is easily compensated for in other sectors of the spine, so motion can be practically free and stature return

to the vertical. Recovery takes place with but little impairment of function. Ankylosis of bodies, the ideal process of resolution in inflammatory spinal disease, is "a consummation more devoutly to be wished" than an orthopedic operation designed to splint the spinous processes.

**Infectious Arthritis of the Spine in Adolescents.** How many of our "star" cases of a decade ago who recovered from hip disease with perfect function have proved, in these days of the roentgen ray, to have been more or less typical instances of Perthes's disease? We encounter occasionally adolescents with backache, with a slight projection of one or more vertebral spines, giving a history of mild onset and more or less tranquil course. When they occur in subjects who are large and vigorous the abnormal projection is more noticeable. I have seen two girls of fifteen years, one of them almost six feet tall, whom I treated for lumbar spinal disease; they both recovered in a year, but neither pain nor muscular spasm nor recurrence of symptoms have appeared for eight years. An insignificant kyphosis and a slightly restricted range of side bending are the only sequelæ of these two lesions. Will a further study of these cases by the roentgen-ray indicate a mild or "quiet" spinal disease, an infectious osteochondritis juvenilis? It will be remembered that in the ossification of each vertebra a thin, flat, circular epiphyseal plate of bone is formed in the layer of cartilage on the upper and under surfaces of the body. The age at which this occurs is twenty-one years and the upper plate is thicker than the lower; all ossific centers become joined and the bone is completely ossified between the twenty-fifth and the thirtieth year of life. The probability occurs that we may be able to demonstrate lesions in this circular plate analogous to the trophopathies of osteochondritis.

**Treatment.** The treatment of infectious arthritis of the spine is essentially mechanical. A plaster jacket and rest in bed are necessary to control symptoms during the acutely painful stage. To prevent deformity in certain cases a Bradford frame may be used. Without immobilization there is always a possibility of extension of the process. Braces are indicated for a more or less prolonged period to control recurrences. A few of my patients are more comfortable in jackets applied while reclining on a sacral support. This can be explained by an induction of the normal lumbar curve with a coincident separation of the anterior lips of the inflamed vertebræ. One objection to the jacket spica in women seems to be the present shortage of household servants. This difficulty may be met by periods of rest in bed, alternating with short periods of immobilization in light spicas. Full-length jackets extending to the trochanters or including a few inches of thigh on the painful side are most comforting.

The portals of entry of these infectious arthritides of the spine

have painstakingly been looked after. Two years ago all our cases were subjected to rigid scrutiny so fashionable at the time. No single case of mine of infectious arthritis of the spine has been cured by the extraction of teeth or the removal of bridges. Nothing herein should be construed, however, that my patients suffering from backache have not been relieved by oral and throat hygiene by removal of the pelvic or osteomyelitic foci, etc.

The metastatic spinal infections, such as typhoid, uterine infections, some staphylococcemias, etc., are essential sequelæ of saturation of the blood, with virulent bacteria in great numbers. The course, being limited by this period of virulence, is usually of short duration; therefore an operation to fix any portion of such a spine is not indicated.

Light braces of various types, or the Knight spinal brace, have been used during convalescence. The question of massage is to be decided by signs and symptoms. In the acute stages it is contraindicated; in convalescence it occasionally gives relief. The best authorities are not in favor of it. Most of my patients are comfortable without local stimulation by friction, but the cautery, hot baths, heat—in fact, in any form that requires no movement of the spine—is the source of much satisfaction. Violent twistings, pushings, kneadings and so-called adjustments are manifestly harmful; they are followed by tearing of adhesions and loosening of benign excrescences from the edges of vertebral bodies. For the same reasons spa treatments, so popular in Europe, are also contraindicated. The French authors speak very highly of heliotherapy.

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CASE I.—*Staphylococcus Ostitis of the dorso-lumbar Spine.* A Russian woman, aged thirty-eight years, was seen in February, 1916. She had been delivered, with the aid of instruments, five months before. The puerperal discharges two weeks later became hemorrhagic and there was dangerous exsanguination. She was removed to the hospital and remained there for seven weeks. The diagnosis was blood-poison; her temperature rose frequently to 105°, and there were chills. On the twenty-first day she was seized with severe pains in the back, later in the thigh and leg. Temperature subsided gradually. Pain has kept her in bed ever since her discharge from the hospital. Many times a day she complains of severe attacks of grinding in the right sacro-iliac region, the right thigh and leg. Great difficulty was experienced in turning the patient in bed for spinal examination. A rounded kyphosis at the twelfth dorsal and first lumbar vertebræ, with extreme tenderness to either side, over the lateral masses, was easily made out. There was considerable muscular spasm, but no thickening nor abscess. The patellar clonus that was elicited on both sides was most marked on the right. The knee-jerks were

exaggerated, as was the Achilles jerk on both sides. Ankle-clonus was present. Temperature and pulse were normal. A brace was fitted to support the weakened spine and the patient was very definitely improved in a week. Diminished cramps in the legs and almost no backache.

CASE II.—*Arthritis of the Lumbar Spine; Lateral Deviation.* A man, aged thirty-eight years, sent by the neurological service (Mount Sinai) for pain localized over the sacro-iliac joint ("sacro-iliac case"). Local tenderness over the same region, but con-

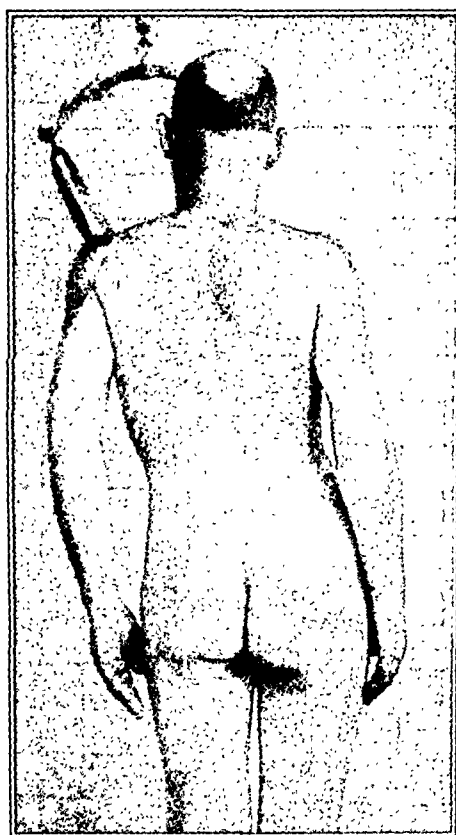


FIG. 1. Case II.—Arthritis infectious lumbar spine.

siderable spasm of the spinal muscles; the roentgen ray detects the lesion to be in the third and fourth lumbar bodies, with lipping of the edges. Three years before he had been in bed for a week and unable to work for three months on account of a right sciatic neuritis; three perineural injections were then given. Patient remained well. Three months before coming under my observation the symptoms returned and were treated by means of a sacro-iliac belt. This did not prevent the gradual increase of a well-marked list of his spine to the left. The pain gradually increased also and was successfully controlled by means of a jacket applied with the aid of a hip rest, extending half-way to the knee.

CASE III.—*Infectious Arthritis of the Lumbar Spine; Lateral Deviation.* A department manager, aged forty-one years, a man of very nervous makeup, was seen for a severe sacral backache. He had had a slight low-back pain six years before. This illness commenced after a game of tennis four weeks previously. His pain radiated into the buttocks and into the lumbar region, and was agonizing on turning over in bed. Bowels, urine, blood and blood-pressure were normal. He had bilateral weak-foot and marked tenderness over the right sacro-iliac joint. He was kept in bed and his lower back was immobilized in plaster. Five weeks later the examination showed marked stiffness in the lower lumbar region and very definite muscular spasm. He had developed a distinct list to the left. The roentgen-ray then demonstrated that the last lumbar vertebra was decidedly sclerosed; its shadow increased in density and its lateral edges roughened and thickened. It was decided that he was suffering from an arthritis that had begun six years ago. A Knight brace was applied, not without some difficulty, on account of the list of the trunk to the left side. This lateral deformity decreased in a month, and in two months the patient was walking erect and able to do part of his work. There was little pain, the lumbar region was flat and very slight limitation of hyperextension of the hips, previously free. The cautery and continuous wearing of the brace resulted in his return to full duty at his desk in another month.

CASE IV.—*Osteo-arthritis of the Lumbar Spine; Sequel of an Acute Infectious Arthritis.* Postman, aged fifty-five years, complained of many attacks of lumbago lasting a few days. In 1914 he had an acute sciatica, for which a perineural injection was given by a surgeon. This gave no relief and a month later the pain became so severe that he took to bed. The pain was constant and darting in the left hip, the sacro-iliac region and down the course of the left sciatic nerve. I saw him in consultation in February, 1915, and found besides the usual tender sciatic points an absolute rigidity of the lumbo-sacral joint. There was a very marked degree of spasm of the lumbar muscles; hyperextension of the hip was painful and limited by muscular contraction. The other hip motions were perfectly free. A roentgen-ray plate showed that the last lumbar vertebra was atrophic and its upper edge had a moth-eaten appearance on the left half. A plaster spica was applied March 14, 1915, and his pain disappeared in a few days. He had required morphine and codeine for six weeks before that to control severe paroxysms. None has been administered since. He gained in weight rapidly. In June, 1915, a Knight spinal brace was applied. Spasm had disappeared; no pain. He walks sixteen miles a day. In October he presented a stiffness and a lumbar flattening of the normal lordotic curve as the only signs of his previous illness. Two

years later a slight recurrence of pain in the left buttock was controlled by two weeks' rest in bed.

CASE V.—Sam P., aged forty-one years. He denies venereal infection. Two years before coming under observation (in 1916) he was confined to bed for two months by a vicious attack of sciatica. He received four epidural injections and the trouble in the right thigh disappeared. His complaint at that time was of a tearing, burning pain in the right thigh and knee down to the back of the ankle. There was, he said, a good deal of backache,



FIG. 2.—Case V.

but he was certain that no deformity of his back existed. The present illness began five weeks ago with the same symptoms, with the exception of the pain in the leg. In the first week the patient (while under treatment in another hospital) noticed that he became gradually crooked and that his body seemed to point to the left. Liniments and internal medication left him unimproved and he applied for treatment at the orthopedic department of the Mount Sinai Dispensary. He presented a marked lumbar deviation to the left, the spine seeming to center to that side; it was decidedly flat where the normal hollow should be. In every direction that motion was attempted the lumbar muscles stood out sharply in contraction.

There was no temperature. His chief complaint was inability to walk without pain. Roentgen-ray findings: Marked rotation of the lumbar vertebræ, especially the second, the spinous process of which is turned to the left. The last three lumbar vertebræ show lipping of their articular margins. A plaster-of-Paris jacket with a small circle around the thigh afforded great relief at once (January 3, 1918). He reported once a week until February 28, when the jacket was changed for a shorter one. He still presented a well-marked torsion to the left. There was definite resistance to right side bending. Flexion and extension were comparatively free. The lumbar spines were rotated so that the left lateral masses were a little easier to palpate than the right. No kyphosis could be detected, but the spinous processes seemed unusually close to one another. No pain; very little tenderness except on vigorous percussion. We have reason to believe that this patient remained well.



FIG. 3 —Case VI.

CASE VI.—Joe E., a cabinetmaker, aged thirty-five years. Venereal infection denied. Eleven months ago he expectorated a little blood; the sputum and pulmonary examination were negative. Nine months ago he had an attack of lumbago, annoying but not disabling, for three days. Four months ago he had a sudden onset of severe pain in the right buttock, right groin, soon

extending throughout the course of the right sciatic nerve and the lumbar region. He was treated for sciatica, and massage and electricity were given, likewise a generous amount of medicine and many baths. After ten weeks of suffering he applied for treatment at the Mount Sinai Dispensary; he then complained of pain in the right gluteal region and in the sacrum. A well-marked list to the spine was noticeable, muscular spasm was decided and clinically he presented the signs of a lumbar spondylarthritis. A short time after applying a jacket with a thigh ring all symptoms were completely relieved. Five weeks later the jacket was removed temporarily for the purpose of taking a roentgenogram and his trouble returned in a mild form. The spine straightened appreciably. Another jacket was applied, with complete relief. The patient had lost seven pounds, presented a flattening of the lumbar curve, and a left dorsal and a right lumbar deviation. There was marked spasm of the lumbar spinal musculature. The motions of the lumbar sector of the spine were *nil* and the first of these vertebræ were very tender over their spinous processes. Knee-jerks were lively; no ankle-clonus; no Babinsky; no evidence of psoas irritation. Diagnosis: Lumbo-sacral arthritis with spinal deviation. Roentgen-ray findings: A slight flattening out as well as a slight lipping of the surfaces of the bodies of the last two vertebræ. He has never been sick since and has worked steadily (April, 1921).

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## OBSTRUCTION OF THE SUPERIOR VENA CAVA BY PRIMARY CARCINOMA OF THE LUNG.

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### PATHOLOGICAL REPORT

BY RUSTIN MCINTOSH, M.D.,

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IN the years since a case of obstruction of the superior cava was first reported by Corvisart, in 1806, there have been recorded 300 cases of this condition, although many of the reports do not permit of a definite conclusion as to the primary etiology.

First collected by Oulmont<sup>1</sup> in 1856, Fischer<sup>2</sup> in 1901 tabulated 253 cases, to which list Hume added 12 cases from the literature, in Osler's<sup>3</sup> report of 2 cases of his own in 1903. The remaining 17

<sup>1</sup> Soc. méd. d'observation, 1856, t. 3, 463.

<sup>2</sup> Inaug. Dissertation, Halle, a. S., 1904.

<sup>3</sup> Bull. Johns Hopkins Hosp., 1903, 14, 169.



cases in Hume's collection, which comprises 29 in all, had been noted in Fischer's list. Rauth<sup>4</sup> includes all of these, except Fischer's own case, in his tabulation of 277 cases in 1911, but as 1 of Rauth's cases had been reported twice the list then stood at 277 cases. In the past ten years more or less satisfactory evidence of the etiological factor has been obtained in 23 other cases of obstruction of the superior cava, reported by seventeen authors.

In the series noted, Fischer was able, out of 20 cases described as being due to primary carcinoma of the lung, to find definite proof, through reports of the microscopic findings, of caval obstruction due to primary carcinoma of the lung in only 4 of the 20 cases. He also verified 13 reports of cava obstructed by primary carcinoma of the bronchi and added 1 case of his own. All but 2 of these cases involved the right lung or the right bronchus. Fischer's own case involved both primary bronchi, the process being more extensive in the left bronchus. Which particular case report from the literature was accepted by Fischer as one of caval obstruction due to carcinoma primary in the left lung I have not been able to identify from the 252 references that Fischer gives. Rauth added to these figures 2 cases of his own of obstruction of the cava as the result of primary carcinoma of the lung, and a case of "cancer" of the lung is included in Hume's collection. This case reported by Barth,<sup>5</sup> in 1853, while listed by Hume as due to primary carcinoma of the lung, was described by Barth as probably primary in the kidneys, and while called by Barth cancer, was more probably a sarcoma or an adrenal tumor. The "cancerous masses" involved both lungs in this case, especially the left. This case can be omitted as not being one of primary carcinoma of the lungs from the original record. Rauth's 2 cases were both due to carcinoma of the right lung.

We have here, then, reports of the interference with the circulation in the superior cava by "primary carcinoma" of the lung in 23 instances, verified as carcinoma in only 6 of these 23; by carcinoma primary in the bronchi in 14 observations. In only 2 of these 37 was the seat of the malignant process in the left lung or bronchus. This is an interesting fact which cannot be a mere coincidence.

Rauth gives as his opinion that this may be due to the right bronchus being the wider and straighter, the right lung being thus more exposed to injury than the left.

Another explanation, it seems to me, may be in the anatomical relation between the cava and the right lung. Certainly, neoplasm of the left lung is not so uncommon as these figures would seem to indicate. While it is a rare condition it so happens that I have seen 2 cases of malignant involvement of the left lung within

<sup>4</sup> Inaug. Dissertation, Univ. zu Giessen, Borna-Leipzig, Rob't. Noske, 1911.

<sup>5</sup> Bull. de la soc. anat. de Paris, 1853, 28, 4.

the past two months, in neither of which was there any interference with the cava. It is my opinion that neoplasm of the left pleural contents usually causes death of the patient from cachexia, from toxemia affecting the heart, from gross interference with the action of the heart or with respiration before the tumor mass has reached the situation of the superior cava; that, on the other hand, tumors of whatever nature involving the right lung or bronchus, or the anterior mediastinum, primarily will soon upset the circulation in the great veins. In support of this theory is the statement of Fischer that most malignant tumors produce caval obstruction not merely by compression but usually by an actual invasion of the vein. Out of the 18 cases to be certainly identified as primary carcinoma of the lung or the bronchus, Fischer found an invasion of the wall of the cava by the tumor in 10 instances.

The case here reported was one in which the obstruction of the caval flow was recognized early and in which autopsy showed that the obstruction was due to a malignant adenoma apparently taking its origin from the bronchioles and involving primarily the left lung.

Clinically, what impressed me most in this case was the absence of edema of the patient's body below the waist. In spite of puffy face, neck and chest there was no ascites demonstrable and his legs were thin. This discrepancy between the upper and the lower halves of the body has apparently surprised many other observers. Comby,<sup>6</sup> Favre,<sup>7</sup> Achard<sup>8</sup> and Haumeder<sup>9</sup> all express their astonishment over this feature of the disease.

It is of interest to note that the three reports by Comby represent only one patient who survived more than fifteen years after his cava became obliterated and who died of general paresis.

Checking the physical findings during life with the autopsy protocol is always instructive. Some things that we found of interest were:

1. That my note on December 23 for absolute heart dulness corresponds quite closely with the situation of the tumor mass.
2. That the situation in which I heard the heart sounds best, on the same date (fifth right space near the right nipple), does not correspond at all with the position of the heart, which was pushed downward, backward and to the left.
3. That the presence of fluid in the left pleural cavity did not interfere with the signs of consolidation of the left lung.
4. That the signs of consolidation were about equally marked over both lobes on the left, probably from compression of the more or less normal lower lobe by the tumor.

<sup>6</sup> Bull. et mém. de la soc. méd. des Hôp. de Paris, January 8, 1892: *Journal* cited December 15, 1893; Vigouroux et Collet, *journal* cited, 1906, 23, 3e s., 137.

<sup>7</sup> Rev. méd. de la Suisse Rom., Geneva, 1918, 38, 97.

<sup>8</sup> Bull. et mém. de la soc. méd. des Hôp. de Paris, 1896, p. 717.

<sup>9</sup> Wiener med. Wehnschr., 1919, 69, 1622.

In the following clinical report the notes initialed "O'H." represent the findings of the house physician, Dr. O'Hara.

We wish to express our indebtedness to Dr. F. B. Mallory for the preparation of the photomicrographs and for his confirmation of the microscopic diagnosis here set forth, thereby adding much to the value of this paper.



FIG 1 -Showing edema of the face and the neck, also dilatation of the veins of the trunk and the right arm.

*Clinical History.* P. B., aged twenty-nine years, white; single. Birthplace, Germany. Admitted December 21, 1919.

*Chief Complaint:* Shortness of breath.

*Family History:* Father living and well in Germany; mother died of heart disease; two brothers and one sister living and well in Germany. No family disease known.

*Past History:* Up to twenty-one years of age he had been in very good health, with the exception of occasional "stomach trouble," which was always relieved by taking sodium bicarbonate. At the age of twenty-one he had scarlet fever and diphtheria simultaneously. Since then he has been in good health up to the present illness. No operations.

*Head:* No headaches; no dizziness. Eyes, ears, nose and throat negative.

*Cardio-respiratory:* No dyspnea; no palpitation; no edema; no cough except short colds in winter season; no pains.

*Gastro-intestinal:* Appetite good; bowels irregular at times; several attacks of indigestion. Had piles fourteen years ago, which disappeared and now appear with the present illness. Some pain with attacks of indigestion and regurgitation of sour material.

*Genito-urinary:* Denies venereal; no nocturia; no polyuria; no dysuria; no burning micturition.

*Neuro-muscular:* No shooting pains; no ataxia; sound sleeper.

*Extremities:* No lameness; no edema up to the present illness.

*Habits:* Drank beer very moderately up to four years ago. No other alcoholic beverages. Smokes two or three cigars daily and very occasionally a cigarette. No drugs.

*Occupation:* Cook.

*Present Illness:* Felt well until October 20, 1919, when he began to feel a little weak, but continued to work. The following day he had a sharp pain which began in the left shoulder, traveled down the left arm and then over the left chest. At this time he was not dyspneic nor did he have palpitation. On October 28 he went to his doctor, who said his condition might be serious and advised a roentgen-ray examination. Doctor told him the roentgen-ray showed enlarged heart and that he must not work for a year. During the following four weeks the patient rested, but not in bed. Gradually he became dyspneic and his legs began to swell. About three weeks ago he developed a cough which lasted about two weeks, during which time there were three days on which he spat up a little blood. Dyspnea and edema have steadily increased, slightly subsiding during the night, only to be progressively worse the following day. For the past twenty days he has not been able to lie on the right side because of pain and inability to breathe.

*Physical Examination:* Patient is a man fairly developed and nourished, lying on his left side in bed and breathing rapidly, with an expression of discomfort on his face. He is rational and quiet; cyanosed.

*Head:* No exostoses; considerable degree of edema about the face, the neck and the lower jaw. Puffiness of both eyelids.

*Neck:* No rigidity; some stiffness due to edema. No abnormal pulsations felt.

*Chest:* Well-formed, equal expansion; considerable edema; veins prominent over the chest.

*Lungs:* Dulness throughout; few high-pitched rales heard over both apices; posteriorly breath sounds decreased throughout. Tactile fremitus diminished over both lungs, more so on the left, posteriorly.

*Heart:* Action rapid; area not made out on account of generalized dulness and edema. Heart sounds distant; no murmurs made out.

*Abdomen:* Somewhat edematous; liver and other organs not palpated, due to edema. Veins considerably enlarged and prominent throughout. No tenderness.

*Extremities:* Arms considerably swollen; legs not so marked as arms, chest and neck.

December 23 (H. W. D.): Marked cyanosis, especially of the left chest and the left upper back. Marked dyspnea. Edema of the face, neck, eyelids and precordia very marked. Legs small. Visible pulsation in epigastrium. Pulse moderately rapid, good volume and tension. Cardiac impulse best felt below the ensiform.

*Heart Dulness:* { absolute, 6.5 cm. to the right: 13 cm. to the left of midsternum.  
relative, 14.5 cm. to the right of midsternum:  
limit of dulness not made out on the left.

Flatness over the entire precordia. Cardiac impulse well felt in neighborhood of and below the right nipple. Heart sounds best heard in the fifth right space, 13 cm. to the right of the midsternum; well heard in the right back near the angle of the scapula. Marked dilatation and distention of the superficial veins from the midline to the right as far as the midscapular line in the right back and from the level of the pubis to the level of the clavicle in front and the spine of the scapula behind.

*Lungs:* Dulness to flatness in the left axilla; area of crepitation and bronchial breathing at left base behind.

*Examination of Urine:* Negative on two examinations.

December 24 (O'H.). The edema is pretty well limited to the head and neck. The blood is going from above downward in the superficial vessels. Signs of fluid in the left chest still present. They seem to have varied from time to time quite a little. Yesterday 1700 cc, removed slowly of clear amber fluid, very evidently a transudate; cell count not taken. Specific gravity not taken. Removal of the fluid gave only a slight temporary relief from dyspnea.

December 24 (H. W. D.). Liver dulness to within 5 cm. below the costal border. No ascites made out. Pulsation over the liver (systolic) apparently expansile in type. Resonance improved over the left back. Pure bronchial breathing and whisper over both lobes (on the left).

(O'H.). Patient seemed more comfortable this evening. Chest tapped again and yielded 1200 cc, 130 cells per cu. mm. Very light trace of albumin. During the last of the time the needle was in the chest, and for about twenty minutes afterward, the patient had what seemed to be an anginal attack of pain in the left chest and down the left arm, relieved somewhat with nitroglycerine.

December 25 (O'H.). Chest tap again attempted; no fluid obtained this time.

December 26 (H. W. D.). Edema of the lungs on the right side, with tracheal rales. Heart has not moved to the left as the result of the removal of the fluid from the left pleura.

December 29 (O'H.). Although the patient was better for the past two days, subjectively, he says he does not feel quite so well

this morning. Dr. Larrabee's blood report is posted on December 26 on the laboratory sheet.

(H. W. D.). The left border of the heart is not percussible on account of dulness of the left chest. Right border 8 cm. from the midline. Sounds short, rapid, slightly irregular and of poor quality, with a friction-like sound accompanying the first sound just to the right of the sternum in the 5th-6th space. Left back dull, flat at base. Bronchial breathing and rales at both apices more marked on the left and diminishing in intensity, but not in character, as the left base is approached. There is doubtless still considerable fluid in the left back. Consolidation of the entire left lung apparently persists. Edema of the right lung for the past three days. Expiration now harsh over the right base.

January 2 (H. W. D.). Increase in degree of bronchial expiration of the right lung. Exquisite bronchial breathing over the entire left lung. No apparent fluid in the left base behind. Gallop rhythm over what appears to be the heart apex at the right nipple. Liver dulness extends 8 cm. below the costal margin. Liver slightly tender; no evidence of ascites. No edema of the legs.

January 3 (O'H.). Patient has now had 90 grains KI i. d. for a week, with no apparent improvement. This goes a long way toward ruling out gumma and makes aneurysm rather unlikely. Although the patient has been slightly better at times, he is taking a progressive downward course.

January 5 (O'H.). Patient has gone downhill rapidly in the past two days and died at an early hour this morning. Wassermann reported strongly positive.

*Diagnosis:* Mediastinal carcinoma. Obstruction of the superior vena cava.

#### BLOOD CHART.

December 26, Red corpuscles	3,000,000	Neutrophil polynuclears	87½ per cent.
White corpuscles	7,000	Eosinophils	½ " "
Hemoglobin	60 per cent	Lymphocytes	4½ " "
		Large lymphocytes	7½ "

No mast cells; no nucleated reds; platelets diminished much; reds show only slight changes.

**Pathological Report.** Autopsy, January 6, 1920, thirty hours post mortem. Body length, 170 cm. Age, twenty-nine years.

The body is that of a rather poorly developed and poorly nourished white male. Rigor mortis is present in moderate degree in all the skeletal muscles, and there is a deep lividity of the dependent portions and of the left side of the face and neck, with a light, blotchy lividity of the left side of the chest. The pupils are round, regular and equal, measuring 0.5 cm. in diameter. The face and neck are bloated, the chest large and the arms and legs thin and emaciated. There is marked edema of the left side of the scalp, face and the upper portions of the neck, of the outer portion of the

conjunctiva of the left eye and of both sides of the base of the neck and shoulders, with definite emphasis on the left side. The edema does not extend to the arms and is not found below the level of the second rib in front or below the spine of the scapula behind. There are several veins visible in the skin of the right side of the chest. Two particularly large trunks pass downward from the region of the right axilla and the right infraclavicular region respectively, joining at the level of the costal margin to form one large trunk

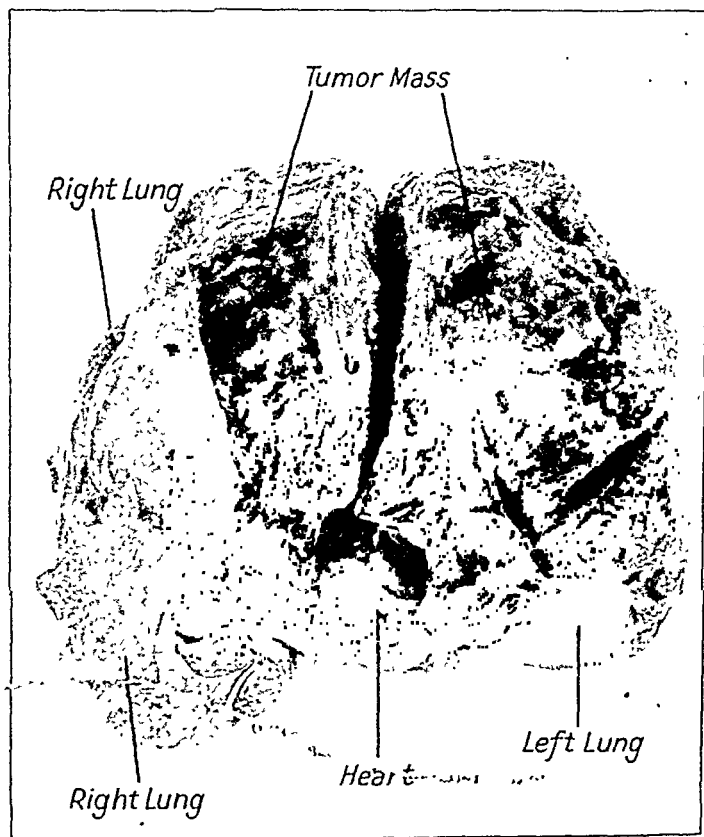


FIG. 2.—Thoracic organs removed entire. The tumor has been split in the center.

which continues downward to a point 2 cm. to the right of the symphysis pubis, where it disappears. In addition there are many areas in the skin of the chest on both sides where groups of smaller venous branches are enlarged and stand out conspicuously under the skin, these areas being more marked on the right than on the left. There is no caput medusæ.

*Peritoneal Cavity:* The subcutaneous fat is small in amount. There is moderate edema of the subpectoral spaces. The peritoneum is everywhere smooth and glistening. In the pelvis there

are about 50 cc of clear, yellowish fluid. The appendix, which measures 4 cm. in length, is firmly bound to the posterior abdominal wall in a retrocecal position, its tip pointing downward and outward. The omentum and mesentery contain little fat and the mesenteric lymph nodes stand out conspicuously, though they do not appear to be enlarged. The liver border extends 8 cm. below the costosternal angle in the midline, 5.5 cm. below the costal margin in the right nipple line. The diaphragm reaches to the level of the 5th rib on both sides.

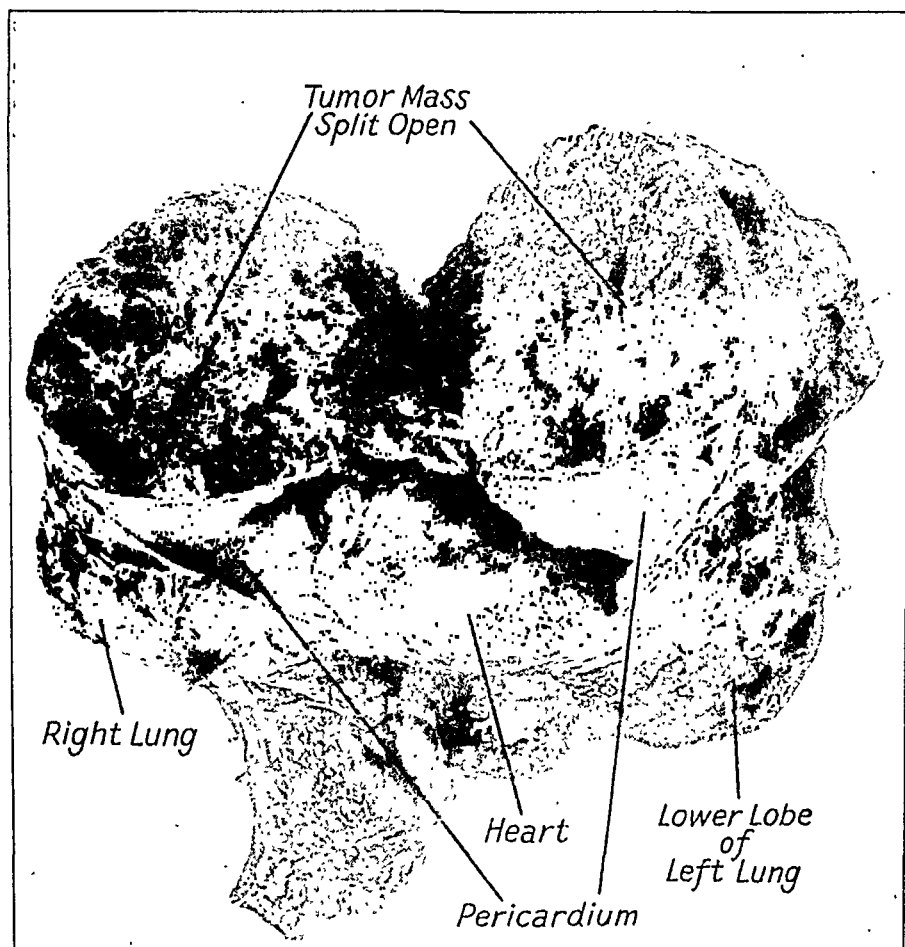


FIG. 3.—Tumor mass spread apart from the central cut, showing position of the heart.

*Pleural Cavities:* On removal of the sternum and ribs a large tumor mass is found occupying the anterior mediastinum, its anterior surface lying directly against the sternum and ribs. Its anterior aspect is roughly circular in shape, the center lying somewhat to the left of the median line. It extends in the median line from a point 1 cm. below the level of the top of the manubrium sterni to a point 19 cm. below, and laterally 5 cm. beyond the midline on the right, 12 cm. on the left. It covers the precordial area completely



and parts of the pulmonic areas, so that from the front only the lateral portions of the right lung and the lower lobe of the left lung can be seen. Its anterior surface is firm and coarsely nodular and grayish-white in color. Over the anterior surface of the left upper lobe the tumor has extended into the intercostal spaces and is firmly adherent to the periosteum of the second and third ribs. There is no erosion of the bone substance.

The left pleural cavity contains many friable, fibrinous adhesions throughout, most marked about the upper lobe and between the upper and lower lobes. By these adhesions the pleural cavity is divided into an upper and a lower cavity, the former containing 300 cc (estimated) of clear, amber-colored fluid, the latter containing 520 cc (measured) of a similar fluid. The bloodvessels beneath the parietal pleura are markedly dilated and stand out prominently as a fine network of innumerable branching and anastomosing trunks. In the parietal pleura of the posterior thoracic wall on the left there are five small circular areas of whitish tissue similar in appearance to the tumor tissue, the largest measuring 0.5 cm. in diameter. The right pleural cavity contains a few fibrinous adhesions anteriorly in the vicinity of the tumor and 1000 cc (measured) of clear yellow fluid. Its parietal surface presents a picture of vascular dilatation identical with that described on the left.

The heart is pushed downward, backward and to the left. On account of the presence of the tumor the pericardial cavity is not investigated *in situ*.

The thoracic organs are removed *en bloc*, the esophagus and great vessels being severed at the level of the diaphragm. The tumor mass is incised in the sagittal plane in the midline, revealing the heart and aorta lying against its posterior-inferior surface. The cut surface of the tumor thus disclosed is oval in shape, the long diameter lying parallel to the axis of the body and measuring 19 cm., the short diameter measuring 11 cm. At the periphery of the area there is an irregular zone of smooth, fairly firm, uniform tissue, in places 1 to 2 cm. in depth, in others barely perceptible. Internal to this there is a zone of soft, red or gray and red tissue representing varying degrees of necrosed tumor tissue. The center of the area is of the appearance and consistence of baked Indian pudding. The tumor mass as a whole is soft, fragile and extremely difficult to handle.

The tumor is removed from the adjacent normal structures by sharp dissection. The heart, aorta, right lung and lower lobe of the left lung are easily identified and separated. The growth of the tumor has displaced the pulmonary vessels downward and backward and has greatly lengthened the superior vena cava and innominate veins and the innominate, carotid and subclavian arteries. The upper lobe of the left lung is so extensively invaded that there is merely a narrow margin of the lung tissue on the posterior and

superior aspects. The vessels and bronchial branches here disappear into a mush of necrotic tumor tissue.

The superior vena cava is opened longitudinally and is found to contain a soft, friable, purple and pink thrombus running its entire length, the lower end of the thrombus projecting in the shape of a cone for a distance of a few millimeters into the right auricle. The thrombus extends for a short distance into the azygos vein and into the right innominate vein, runs up the left innominate vein as far as its bifurcation and continues up the left internal jugular vein as far as it can be reached in the neck. All the veins of the superior mediastinum, neck and shoulder regions are enormously distended and the tributaries of the subclavians running to the scapular and pectoral regions are especially conspicuous. The arteries, aside from their displacement, are not remarkable.

*Pericardial Cavity:* Contains about 15 cc of clear, yellow fluid.

*Heart:* Weight, 255 gm. The organ is small and rather flabby. Over the auriculoventricular and interventricular grooves there is a small deposit of pale fat. On opening the right auricle a thrombus is seen projecting for a short distance into its lumen from the superior vena cava as described above. The muscle on section is of a pale brown color. The endocardium and valves are not remarkable. The ascending portion of the aortic arch and the coronary vessels are free from sclerosis.

Measurements:

Tricuspid valve, 12.5 cm.

Pulmonary valve, 7. cm.

Mitral valve, 10.5 cm.

Aortic valve, 7 cm.

Left ventricle, 1.3 cm. in thickness.

Right ventricle, 0.4 cm. in thickness.

*Lungs:* The left upper lobe is extensively infiltrated with tumor tissue, which has replaced practically all the lung tissue. The lower lobe is gray-green in color, somewhat compressed, elastic and crepitant throughout on palpation. On section it is for the most part greenish-purple in color and translucent, with a smooth, elastic, rather dry surface from which but a small amount of frothy fluid can be expressed. The bronchioles are dilated and closely packed together. About some of the bronchioles in the outer portion of the lobe there are small, irregular, raised areas of reddish-gray, opaque, rather firm tissue. A few of the bronchial branches contain a small amount of mucopurulent secretion. The larger bronchi and vessels are not remarkable. The right lung is somewhat firmer and more nodular than the left. On section it presents a picture similar to that of the left lower lobe, with atelectasis, bronchiectases and scattered areas of partly organized bronchopneumonia. In addition it is edematous and congested, particularly in the upper lobe.

*Spleen:* Weight, 80 gm. The organ is small and firm. The capsule is thin and finely wrinkled throughout. On section it presents a smooth, fairly firm surface, reddish in color, in which the connective-tissue markings are rather prominent. A moderate amount of pulp scrapes away on the knife.

*Gastro-intestinal Tract:* Negative.

*Pancreas:* Negative.

*Liver:* Weight, 1590 gm. The organ is of average size and consistence. On the anterior-superior aspect of the right lobe a dome-shaped mass, 1.5 cm. in diameter, protrudes  $\frac{1}{2}$  cm. above the surrounding surface. It is of fairly firm consistence and appears pale gray through the liver capsule. Section through the mass shows a round, unencapsulated and infiltrating area of smooth, fairly firm tissue, pale gray in color, save at the center, where there are a few irregular areas of reddish softening. A similar but somewhat smaller nodule occurs in the left lobe, and on section of the liver a third mass, the size of a large pea, is found embedded in the liver tissue 1.5 cm. below the capsule. The cut surface of the liver is red-brown in color, and in it the lobular markings stand out distinctly, the portal areas being dark red in color. The gall-bladder is thin-walled and contains about 20 cc of dark brown, viscid bile.

*Kidneys:* Weight, 350 gm. The organs are somewhat large, the consistence being normal. The capsule strips readily, leaving a smooth surface. On section the cut surface has a congested appearance. The markings are distinct, the cortex varying from 0.6 to 1 cm. in width and the glomeruli showing as red, translucent points. The pelves and ureters are not remarkable.

*Adrenals:* Negative.

*Bladder:* Negative.

*Genital Organs:* Negative.

*Aorta:* The surface is for the most part smooth, with but a few scattered areas of yellowish thickening. There is no calcification. The vessel stretches with considerable elasticity.

*Anatomical Diagnoses:* Malignant neoplasm of the mediastinum and the upper lobe of the left lung, with metastases to the pleura and to the liver. Thrombosis of the superior vena cava, the right and left innominate veins, the azygos vein and the left internal jugular vein, with establishment of a collateral circulation by the veins of the pleura and the skin of the chest and abdomen. Cachexia. Edema of all the tissues above the level of the junction of the second rib with the sternum. Bronchopneumonia of the right upper and lower and left lower lobes. Atelectasis. Bronchiectasis. Acute serofibrinous pleuritis, bilateral. Congestion of the kidneys. Slight arteriosclerosis.

*Bacteriology:* Heart's blood: Negative.

Right lung: Pneumococcus, Type II, and Staphylococcus aureus.

Left lung: Pneumococcus, Type II.

Right Bronchus: *Staphylococcus aureus*.

Left Bronchus: Contaminated.

*Microscopic Examination:* Postmortem changes throughout.

*Heart:* Negative.

*Lung:* Bronchopneumonia, with an exudate of polymorphonuclear leukocytes, a large proportion of endothelial leukocytes and small amounts of fibrin. A few diphtheroid organisms. Marked edema of the connective-tissue septa, with a small amount of inflammatory exudate. Organizing pleuritis. Two small foci of tumor tissue.

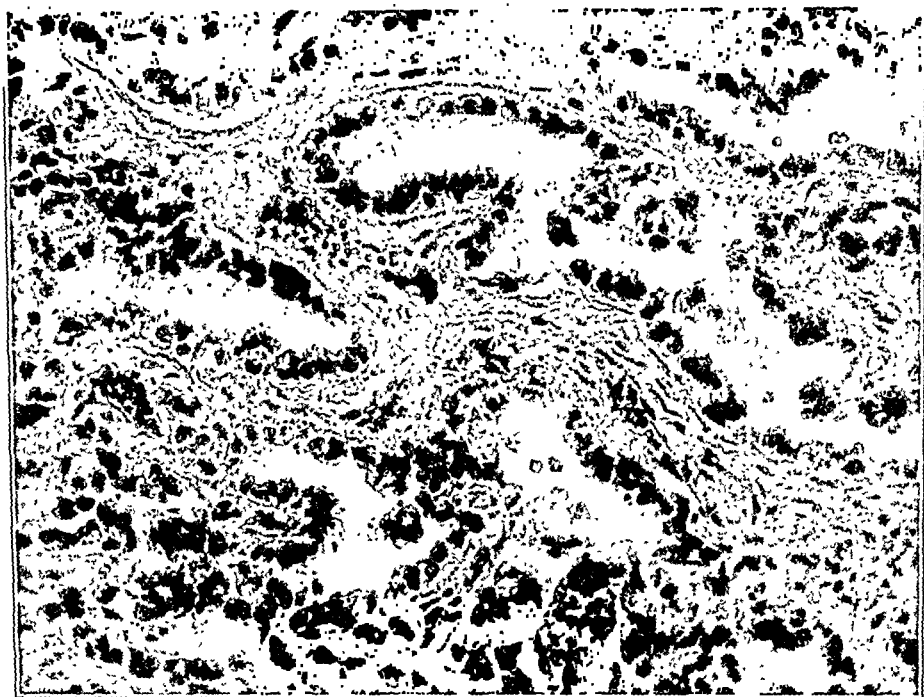


FIG. 4.—Section of tumor in the lung, showing gland-like cavities lined with cuboidal epithelium. The stroma is moderate in amount.  $\times 200$ .

*Tumor I:* A rapidly growing epithelial tumor, suggesting origin from the bronchial or the alveolar epithelium. The tumor cells are arranged in groups suggesting narrow tubes and walls of alveoli. They are single-layered and of rather irregular shape, and occur in groups bound by a loose edematous stroma with young, large cells. The tumor cells are cuboidal or cylindrical in shape and deep blue in color. The nucleus is round or oval with a fine chromatin network; the cytoplasm consists of fine blue reticulum. Mitotic figures occur frequently. Postmortem degeneration is marked. There are scattered areas of necrosis.

*Tumor II:* Same with a better nuclear stain.

*Tumor III:* Same. The alveolar structure is plainer. Mucous connective tissue, which in places is infiltrated with lymphocytes.

*Superior Vena Cava I:* The lumen contains a thrombus, partly of tumor tissue, partly of fibroblasts and fibrin. The vessel wall is edematous and the surrounding tissue consists of edematous connective tissue infiltrated with lymphocytes and endothelial leukocytes, resembling the mucous connective-tissue stroma of the tumor.

*Superior Vena Cava II:* Same. Only a few tumor cells in the lumen.

*Superior Vena Cava III:* Lumen entirely filled with thrombus. Organization of the periphery is fairly well advanced. Areas of invading loose connective tissue.

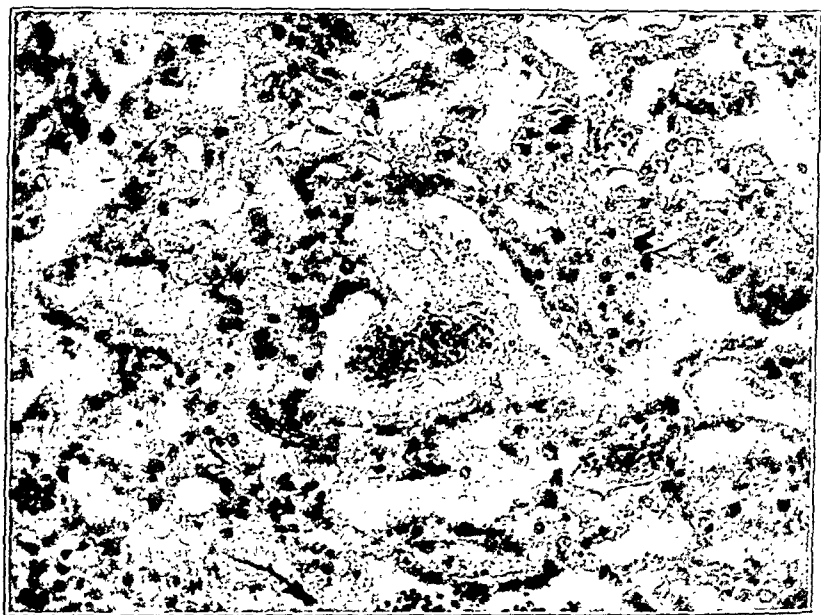


FIG. 5.—Section of metastasis in the liver. The lining epithelial cells are flatter in character, the stroma slighter.  $\times 200$ .

*Vein:* Smaller vessel. Picture same as superior vena cava III.

*Spleen:* Small amount of hyalin in the lymph follicles. Congestion.

*Stomach:* Thrombosis of a vein.

*Intestine:* Negative.

*Pancreas:* Negative.

*Liver:* Congestion and edema. A round area of tumor tissue is compressing the liver tissue into concentric rings of flattened cells. No fibrous capsule about the tumor. The tumor shows a similar picture to that described above.

*Kidney:* Congestion.

*Adrenal:* Dilated veins in medulla. Edema of surrounding connective tissue with atrophic fat.

*Aorta:* Few small atheromata.

*Bone-marrow:* Marked postmortem change.

*Microscopic Diagnoses:* Primary carcinoma of the lung with extension into the superior vena cava and metastasis to the liver. Thrombosis of the superior vena cava. Bronchopneumonia. Pulmonary edema. Organizing pleuritis. Congestion and hyalin changes in the spleen. Congestion and edema of the liver, kidneys and adrenals. Arteriosclerosis.

NOTE.—This is not a “joint article,” but a clinical paper, plus a pathological report. The pathologist never saw the clinical paper; he is not responsible for the opinions expressed therein, and since he never saw the patient during life, any clinical opinions must of necessity have been mine, except where noted as being O’Hara’s. I have therefore retained the expression of “my” opinions.

H. W. D.

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## AN ENDOCRINAL FACTOR IN GENERAL PARESIS.

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It has for many years puzzled psychiatrists why it is that of the great number of persons who are infected with syphilis only a few, probably less than 3 per cent of the total number, eventually develop general paresis. In seeking an answer to this question it is necessary to proceed along two natural lines. The first one is to show, if possible, that the difference rests in the spirochete—that there are strains of spirochete and that the ultimate development of general paresis in a patient depends upon infection with a certain syphilitic strain. The second is to seek out inherent peculiarities of the individual which would cause that individual to develop the paresis.

It is now generally acknowledged that general paresis follows in habitual quasi-constant fashion the syphilis of the benign initial type, and recognized that the likelihood of the development of general paresis in a case of syphilis is in inverse proportion to the occurrence of peripheral ectodermic reaction in the earlier course. The individual who after luetic infection does not show strong ectodermic lesions is more liable eventually to develop paresis. This clinical observation alone does not help to settle the question whether a special neurotropic strain of spirochete determines the paresis or whether the inherent constitutional condition of the individual determines it. The data which I have been able to bring together bear out the second phase of the question and show that the endocrinal

status of the individual has at least a discernible influence in the situation.

Experimental work has been done by various workers to demonstrate that a neurotropic form of spirochete is distinct from a so-called dermatropic virus.

Wile and De Kruif experimented with material obtained from a living paretic brain, and this material was injected into rabbits. They found that subcultures from the rabbits grew much more slowly and much less luxuriously than those cultivated from early cutaneous or mucous-membrane syphilides.

In 1916 Reasoner was able to demonstrate fixed differences in various strains of syphilis as studied in the rabbit. Choroiditis and choreo-retinitis were observed in rabbits inoculated with two different strains of syphilis, and in one strain whose characteristics were not known. In a series of fourteen other strains obtained from chancres and mucus lesions such lesions were not observed.

Milian, writing in 1920, regards it as established that there are different kinds of spirochete, so that the term parasyphilis for tabes and general paresis in his estimation is correct. He believes that the difference between general syphilis and tabes and general paresis is analogous to the difference between typhoid and paratyphoid.

In the past year Marie and Levaditi have reported extensive researches in this field. What they refer to as neurotropic virus they obtained from either the blood, brain substance or spinal fluid of a case of paresis, and their dermatropic virus was in the beginning obtained from a chancre. They report differences as regards inoculation time in rabbits, type of lesion produced, ability of transference from rabbit to monkey and from rabbit to man, and in immunology. They conclude that the spirochete of general paresis must be considered as a different variety from the spirochete causing cutaneous and visceral syphilis.

Though others have believed that in experimental syphilis differences in virulence as well as differences in the period of incubation, and in the character of the lesion can arise through difference in technic, the weight of evidence is in favor of the existence of strains of spirochete.

Yet even granting that there are strains or types of virus differing in evasiveness or predilection for certain tissues the individual resistance of the infected person must still be studied as influencing the form which a syphilitic infection may take.

The almost total absence of general paresis among Arab syphilitics has long attracted attention. Poret and Sengis point out that not even the stress of years of service at the front brought any increase in general paresis among the Arab troops. At Algiers, notwithstanding the extreme prevalence of syphilis, they encountered but one instance of general paresis, and that was of such mild form that the Arab officer was able to serve for more than three years at the

front after the onset of the disease. In China and Japan osseous syphilis is frequent, but nervous syphilis is rare. It would take one into speculative fields to attempt an exact correlation between racial and endocrinal factors, as we at present know them, and that attempt will not be made here.

In the New York State Hospital statistics, though the admissions to the State Hospital show the sexes to be almost evenly represented—for the year ending June 30, 1917, there were 1047 male admissions and 1037 female—there is a marked difference in the number of admissions for paresis—almost three times as many men as women (72 men and 28 women). Since we have no statistics to prove that syphilis occurs more frequently in men than in women, the far higher occurrence of paresis among men stands without explanation. One is led to wonder if the endocrinal condition of men is more favorable toward syphilis taking the paretic form than the endocrinal status of women.

Thus peculiarities concerning the occurrence of paresis as regards race and sex can be cited, and it is probably true that endocrinal factors lie at the base of each.

Long since struck by the infrequency of associated status lymphaticus and paresis I examined a group of 82 unselected cases of general paresis in the Manhattan State Hospital for the purpose of finding what percentage of them gave the signs of status lymphaticus and, further, to classify them into grades according as their external appearance and makeup removed them from the status lymphaticus type.

Status lymphaticus can be safely made a matter of inspection alone, for it can be recognized by the slenderness of the long bones, by the absence of facial and sterno-pectoral hair and by the presence of a feminine type of demarcation of pubic hair. Also the axillary and pubo-anal trichosis is reduced in amount. In the status lymphaticus individual there is a feminine-like rounding or molding out of the contour of the arms and legs. This feature becomes less conspicuous in the individuals of middle life. Though additional signs of status lymphaticus are found only on the autopsy table, it is the opinion of pathologists that the margin of difference in ratios obtained clinically and at autopsy is negligible. I examined the cases of paresis by inspection alone and made my classification on the points above mentioned.

Of the 82 individuals I found only 2 outspoken cases of status lymphaticus. Fifteen, Group 2, showed a low degree of trichosis, not accompanied by the skeletal proportion or other features of the true status lymphaticus condition. Twenty-six cases, Group 3, were average in trichosis. In the fourth group, made up of 21 cases, there was great and more than average trichosis, with the hairy development limited to the body areas normally showing hair in the males. In yet a fifth group, made up of 18 cases, are found the individuals in whom the hairy coat is very excessive, in whom the



distribution leaves almost no part of the body free. Thus, out of 82 cases of paresis only 17 fell below the average in trichosis while 39 ranged above the average. First, it is clear that there was a low occurrence of status lymphaticus among the 82 cases of paresis. Among 5652 autopsies in Bellevue Hospital, Symmes has reported 457 cases of status lymphaticus. This rate pertains to both sexes considered together. The rate for men considered alone is higher—10 per cent. The occurrence of only 2.43 per cent among male paretics is in sharp contrast. The great percentage of the hypertrichotic types among the paresis cases is striking.\*

In Group 3, the average trichosis group, the duration of symptoms from onset to the death of the patient (14 cases dead) averaged 36.7 months and for Group 2, hypotrichotic, but not status lymphaticus (7 cases dead), the duration of symptoms averaged thirty-six months. Neither of the 2 status individuals has died. Regarding the hypertrichosis groups the average for Group 4 (12 cases dead) was 33.5 months and for Group 5 (8 cases dead) twenty-eight months. Thus the average duration is appreciably reduced for the groups showing hypertrichosis and most reduced for the group showing the hypertrichosis in greatest degree. Also, in the hypertrichotic groups (4 and 5) 50 per cent of the cases died in less than two years from the onset of the disease, while of Groups 2 and 3 (average and hypotrichosis) only 29.5 per cent died in less than two years. In addition, of these latter two groups 43 per cent lived more than three years after the onset while of Groups 4 and 5 (hypertrichotic) only 30 per cent lived more than three years. These percentages in conjunction with the figures previously put down appear to indicate that general paresis besides showing a greater incidence in individuals with hypertrichosis on the average runs a more rapid course in such individuals.

Regarding the first of these apparent relationships, some will want to suggest that status lymphaticus cases and near-status cases are inherently less liable to lead a life conducive to infection with syphilis, and that this would be an all-important factor in preventing that type of individual from appearing later in the same proportion among paretic cases. No such explanation, however, explains the data bearing on the second phase—namely, that the course of the paresis is hastened. It was impossible to tabulate the antiluetic treatment which these cases had had during their period of luetic infection. They were not under treatment once they had progressed to the point of commitment into the State Hospital. They were, as before stated, unselected cases, and it was thought possible to consider the previous antiluetic treatment as a common factor in them, probably, if known, surprisingly of an average all told.

\* In addition it has been possible to correlate the groups with the duration of the disease in a portion of the series. A majority of the clinical examinations were made over a year ago, and recently it was possible to record the length of the disease in a series which had died.

Symmers mentions the almost constant occurrence of hypoplasia of the suprarenal cortex in subjects of status lymphaticus. Apert has elaborated his observations regarding the clinical manifestations of suprarenal hyperplasia according to the age of the individual, and believes that for all ages hypertrichosis is a symptom of suprarenal hyperplasia. These references, with numerous others which could be added, show that observations to date connect hypertrichosis with hyperplastic suprarenal functioning. Trichosis in an individual becomes a measure of suprarenal valence and excessive hypertrichosis probably marks the type with the strongest suprarenal chemistry. This, applied to the figures which I have previously given, suggests that heightened suprarenal functioning in the individual is one factor to influence the syphilitic infection in him to assume the special general paretic type and to hasten the course once it is started.

Briefly the conclusions are: (1) The endocrinal status of the individual has a discernible influence in determining whether, once infected with syphilis, he is likely to develop paresis; (2) status lymphaticus is rare among male cases of paresis and is seen less frequently among paretics than among autopsied hospital male cases; (3) individuals who have low suprarenal functioning appear to develop paresis less frequently than strong suprarenal individuals; (4) the course of general paresis on the average varies in rapidity directly with the suprarenal strength of the individual.

**Discussion.** These observations lead me to believe that an estimation of the suprarenal status of an individual at the outset of general paresis can become not alone an index of the probable course of the disease, but also an index of the individual's probable response to treatment—that the weak suprarenal type can be held in check by medication in a manner quite impossible with his opposite in type. Once we accept this observation one's approach in the treatment of paretic cases would be to change by some means the chemistry of the individual in order to pervert any existent suprarenal predominance. This effort would be an adjunct to the usual anti-luetic treatment and in no sense a substitute for it. Although methods to alter suprarenal predominance are not known with scientific accuracy at the present time, certain lines of endocrinal therapy suggest themselves and may prove successful. This phase of the question needs long clinical observation, and must be held for later reporting.\*

\* Symmers states that status lymphaticus was found six times more frequently in men than in women. In one series of 249 cases of status lymphaticus, 212 were men and 37 women. On the same proportion, of the 457 cases discovered in the larger series 392 were men and 65 women. The sex of the 5676 cases autopsied is not recored in Symmers's article or ascertainable with an absolute exactitude. However, as in Bellevue Hospital 67 per cent of the autopsies are on males, it is fair to estimate that 3787 were men and 1865 women. Two hundred protocols of autopsies in 1908, 100 in 1910 and 200 in 1914 were reviewed in order to arrive at the average percentage 67 per cent. Therefore, out of 3787 autopsies of men, 392 cases of status lymphaticus were found, an occurrence of 10.35 per cent.

The courtesy of Dr. Marcus B. Heyman, superintendent of the Manhattan State Hospital, in permitting me to examine and report concerning cases in that hospital is gratefully acknowledged.

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**CHRONIC LYMPHATIC LEUKEMIA ASSOCIATED WITH EXTENSIVE AMYLOIDITIS, ADVANCED NEPHRITIS AND ORAL SEPSIS.**

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THE following case is of particular interest, because it exemplifies one of the more unusual conditions which occasionally are associated with leukemia—namely, amyloid infiltration of the viscera in conjunction with an advanced nephritis. The patient was admitted to the medical service of Dr. Leroy H. Briggs at the San Francisco City and County Hospital, and I am indebted to Dr. Briggs for the following clinical history.

**Case History.** The patient was a married woman, aged forty-eight years, of American birth, who entered the hospital in April, 1920, complaining of chronic bronchitis. The family history and the past history were unimportant. The present illness dated from 1917, when she was treated at the Lane Hospital for leukemia. The following data, covering a period from November, 1917 to July, 1918, were obtained from the records of the Lane Hospital. The first recorded blood examination was made in the out-patient department on November 6, 1917:

Hemoglobin, 55 per cent. Red blood cells, 2,230,000. White blood cells, 10,000.

Differential count: Polymorphonuclear neutrophils, 34 per cent.; large mononuclears, 5 per cent; small mononuclears, 5 per cent; polymorphonuclear eosinophils, 1 per cent; polymorphonuclear basophils, 1 per cent; myelocytes, 3 per cent. One normoblast was present.

On entrance to the Lane Hospital in December, 1917, the outstanding findings were as follows: The patient was very pale; there was a loud blowing systolic murmur heard all over the precordium, although there were no palpable peripheral lymph nodes; the spleen was definitely enlarged and hard, extending well below the costal margin on the left to within 1 cm. of the umbilicus. The urine showed a large quantity of albumin and some hyaline casts. The phthalein test for renal function showed an output of 35 per cent of the dye in two hours. There was no Bence-Jones proteinuria. The subsequent findings and procedures in the Lane Hospital were as follows:

December 5, 1917. Blood examination: Hemoglobin, 50 per cent; red blood cells, 1,885,000; white blood cells, 25,300.

The differential count showed 71.5 per cent of lymphocytes with 3.5 per cent of myelocytes.

Between December 14 and June 1 the patient was given thirty-five roentgen-ray treatments over the spleen.

February 12, 1918. Blood examination: Hemoglobin, 55 per cent; red blood cells, 3,170,000; white blood cells, 38,000.

The differential count showed 80 per cent lymphocytes with 3.5 per cent myelocytes. The Wassermann reaction in the blood serum was negative. The stool examination and the gastric analysis showed nothing pathological.

July 29, 1918. Blood examination: Hemoglobin, 60 per cent; red blood cells, 3,810,000; white blood cells, 15,000.

The differential count showed 50 per cent lymphocytes and no myelocytes. The patient was discharged shortly after the last blood examination and appeared subjectively much improved. The discharge diagnosis was chronic lymphatic leukemia and mitral insufficiency.

Between this time and her admission to the San Francisco City and County Hospital in April, 1920, she appears to have been in at least fair health. On her admission to the last-named institution her chief complaint was chronic bronchitis. On physical examination the following essential points were noted:

The patient is a middle-aged woman with marked pallor of the skin and mucous membranes. There are a few purpuric spots over the forearms. There is extreme dental caries and pyorrhea alveolaris. The heart is not enlarged. There is a loud, blowing, systolic murmur over the precordium, maximal at the apex. The peripheral vessels are not palpable. The blood-pressure is 130 systolic over 45 (?) diastolic. The spleen is large, firm and found well below the left costal margin almost to the umbilicus. The liver is not palpable. The urine examination shows a urine of low specific gravity, 1.005. No sugar or Bence-Jones proteinuria are found. Albumin is present in large quantities and many finely granular and hyaline casts. The phthalein test for kidney function shows

almost complete suppression of the dye in the usual two-hour period—there is less than 5 per cent recovered. The urine collected at two-hour intervals during the day and over the whole nocturnal period after the manner of the Mosenthal renal test diet plan for the estimation of the renal function showed a definite fixation of the specific gravity at 1.005 in all the specimens in conjunction with nocturnal polyuria.

Blood examination: Hemoglobin, 20 per cent; red blood cells, 2,024,000; white blood cells, 15,000.

The differential count showed: Polymorphonuclears, 20 per cent; large mononuclears, 6 per cent; small mononuclears, 71.6 per cent; polymorphonuclear basophils, 14 per cent; polymorphonuclear eosinophils, 0; neutrophilic myelocytes, 1.6 per cent.

The blood platelets appeared decreased in number and no normoblasts were seen. There was no poikilocytosis or anisocytosis. During her subsequent course in the hospital the blood picture remained essentially the same as the above outlined count, except for a terminal myelocytic increase to 8 per cent.

On account of the extreme oral sepsis an attempt was made to have the mouth cleaned up by the removal of carious teeth. Following the dental extractions, severe bleeding ensued, which continued for several weeks immediately prior to the patient's death on November 5, 1920.

The salient features of the gross pathology, as revealed by the necropsy performed by Dr. W. A. Perkins, were as follows:

There was a moderate amount of subcutaneous tissue present which was hyperchromatic in color. The heart was slightly enlarged with a normal appearing myocardium. The spleen was considerably enlarged and weighed 250 gm. The capsule was markedly thickened and the surface was smooth and glistening. On section the spleen was found to be firm in consistence and the pulp did not scrape off readily. The liver was not enlarged and showed nothing remarkable on cut section, except that it was pale in color and had a greasy, lardaceous appearance. The kidneys were of equal size, not enlarged, and they presented the same greasy appearance as the cut surface of the liver. The kidney capsules stripped readily and there was no increase of pelvic fat. On section the renal cortex of both kidneys was found to be contracted. The glomeruli were visible as definite white points. On frozen section the glomeruli appeared as homogeneous, solidly acid-staining balls, whereas the renal arteries were encircled by homogeneous, acid-staining material. The bone-marrow obtained from the femur was of a brownish-red color and appeared distinctly increased in amount. The iodine reaction for amyloid was definitely obtained on sections of tissue from the liver, spleen, kidneys and adrenals.

The microscopical study of the tissues confirmed the impression that we were dealing with an extensive amyloidosis of the viscera, and briefly added the following facts:

In the liver the intermediary zone was occupied by an almost complete replacement of the liver cells by a homogeneous staining, structureless material. The spleen showed areas of infiltration of mononuclear cells in great numbers. The Malpighian bodies were less infiltrated with the amyloid than the surrounding structures. The kidneys presented a striking microscopical picture, revealing the lesions of an advanced, diffuse, chronic nephritis in association with an extensive amyloid infiltration. The glomeruli were very prominent and appeared as solidly, acid-staining balls. In many places glomerular adhesions to Bowman's capsule could be made out. The other renal vessels were also involved in the amyloid process and showed a definite replacement of their muscular coat with the waxy, homogeneous, acellular material. The adrenals also presented in an exquisite manner the same amyloid infiltration as noted in the foregoing organs. Another prominent feature of the microscopical study was the presence in all the viscera of clumps of small round mononuclear cells deep in the tissues and usually surrounding the capillaries. The bone-marrow was clearly hyperplastic and the mononuclear elements definitely dominate the cellular picture.

**Comment.** The above case gives rise to several interesting questions which cannot be wholly explained or answered. In the first place, is there any relationship between the leukemia and the amyloidosis? Osler<sup>1</sup> mentions the fact that leukemia is one of the less usual disease conditions in which amyloid infiltration of the viscera is occasionally encountered. Ordway and Gorham,<sup>2</sup> in their recent excellent discussion of the leukemias in *Oxford Medicine*, do not mention amyloidosis as even an occasional pathological finding in leukemia. Amyloidosis is established as associated with chronic suppuration, and consequently is found in tuberculosis, particularly tuberculous osteomyelitis; empyemas of long standing and syphilis. Among the other less common conditions in which it occurs are malarial cachexia, lead-poisoning, carcinoma and leukemia.

Experimentally amyloidosis has been produced in various ways. One of the most successful recent researches is that of Bailey,<sup>3</sup> who produced visceral amyloidosis in rabbits by the injection of cultures of the living colon bacillus over long periods. Hirose,<sup>4</sup> working in Welch's laboratory on a similar problem, failed to produce amyloid disease artificially in goats, dogs and rabbits by using

<sup>1</sup> Principles and Practice of Medicine, 1912, 8th ed., p. 711.

<sup>2</sup> Oxford Medicine, Christian and Mackenzie, 1920, 2, 681.

<sup>3</sup> The Production of Amyloid Disease and Chronic Nephritis in Rabbits by Repeated Intravenous Injections of Living Colon Bacilli, Jour. Exp. Med., 1916, 23, 773.

<sup>4</sup> Experiments in the Artificial Production of Amyloid, Johns Hopkins Hosp. Bull., February, 1918, 29, 40.

<sup>5</sup> The Blood-pressure in Amyloid Kidney Disease, Johns Hopkins Hosp. Bull., August, 1918, 29, 191.

subcutaneous injections of cultures of *Staphylococcus aureus* and turpentine. He concluded, "That the artificial production of amyloid is very difficult and inconstant, even when methods are employed which have sometimes been successful." The same investigator points out from a study of 59 cases of amyloid kidney disease collected from the pathological records of Johns Hopkins and the Bay View Hospitals of Baltimore that in every case studied there was a trace of nephritis with degenerative changes in the renal epithelium of the tubules and scarring of the more affected areas. He believes, although he could not prove it, that the amyloid infiltration itself plays little part as a causative factor in the associated nephritis, and he is inclined to think that the factor which caused the presence of the amyloid is also capable of producing the changes in the kidney substance—in other words, the nephritis. In view of this, those who are adherents of the infectious hypothesis for the etiology of leukemia may find a common explanation of the two conditions in the above case. Furthermore, Hirose made some interesting observations in regard to the blood-pressure in a certain number of the cases he studied. In 15 cases of definite kidney disease in which blood-pressure determinations had been made it was found to be normal or below normal.

A second point for consideration is, what if any relationship existed between the marked oral sepsis which was present over a long period, the amyloidosis, the leukemia with splenomegaly but without generalized lymphatic enlargement, and the advanced nephritis? In a cursory review of the literature I have found no reference to oral sepsis in relation to amyloidosis—obviously our case throws no light on this point. In regard to oral sepsis in association with blood diseases such as anemias, including both the primary and the secondary types, numerous writers have emphasized a frequent clinical concomitance. If any fundamental relationship does exist with the anemias, would it be unreasonable to think that some such relationship might also be present with leukemias?

The inference of a causative connection between oral sepsis and chronic nephritis has been extensively alluded to in the recent medical writing, and will only be mentioned here.

In conclusion the question may be raised by the above case as to whether we are dealing with a true lymphatic leukemia or merely an extreme grade of lymphocytosis in the presence of a chronic infection. Cabot<sup>6</sup> called attention to three groups of cases in which the diagnosis between lymphatic leukemia and the simple lymphocytosis may be in doubt—namely, in pneumonia; following wound sepsis; and finally subsequent to tonsillitis which was accompanied by a general lymphoid enlargement. In all of these condi-

<sup>6</sup> Modern Medicine, Osler and McCrae, 1913, 4, 676.

tions he has seen a lymphocytosis of such an extreme grade that a true lymphatic leukemia was difficult to exclude. Quite recently Sprunt and Evans<sup>7</sup> have also called attention to another group of cases occurring in young adults in which there is found a mononuclear leukocytosis accompanying an acute infection. They point out that this type of case may be difficult to distinguish at times from the onset of an acute leukemic state or of an early Hodgkin's disease. It accompanied upper respiratory infections, and particularly tonsillitis, and in 4 of their 6 cases it was associated with a moderate grade of general glandular enlargement. The blood picture showed a slight increase in the cells of the large mononuclear-transitional group and the presence of many pathological lymphoid forms. All of these cases went to complete recovery, with the return of the differential formula to normal limits.

Obviously, our case cannot be classed with these last-mentioned groups of Cabot and Sprunt and Evans. The only clinical point against the diagnosis of chronic lymphatic leukemia was the persistent absence of general glandular enlargement. The long clinical course of our case, extending as it did over a period of three years, the constant presence of splenomegaly and the study of the necropsy material, with special reference to the bone-marrow, left little doubt that the case was primarily a true instance of chronic lymphatic leukemia with the rather unusual association of extensive amyloidosis and advanced nephritis.

<sup>7</sup> Mononuclear Leukocytosis in Reaction to Acute Infections. ("Infectious Mononucleosis"), Johns Hopkins Hosp. Bull., 1920, 31, 410.



## REVIEWS.

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BACTERIOLOGY, GENERAL, PATHOLOGICAL, INTESTINAL. By ARTHUR I. KENDALL, B.S., PH.D., Dr. P. H., Professor of Bacteriology Northwestern University Medical School. Second edition. Pp. 680; illustrated with 99 engravings and 8 plates. Philadelphia and New York: Lea & Febiger, 1921.

THE many advances in bacteriology during the four years that have elapsed since the appearance of the first edition of this work have been carefully considered in this revised second edition. The chapter on anaërobic bacteria is especially noteworthy, with a well balanced presentation of the various anaërobes found by Weinberg and by Bullock, Henry, McIntosh and others of the British Medical Research Committee to be of such great importance in war wounds. A proper conservatism is maintained in regard to the etiology of influenza, typhus, trench fever and similar acute infections, which with extensive references and the author's suggestive style offer the reader very satisfactory and stimulating presentation. One regrets the omission of consideration of Dreyer's and others work on the quantitative agglutination of the typhoid group and in other places of more specifically detailed technic to guide the student reader. The form of the book, type, illustrations and index are pleasing, though, as is so often the case, one looks in vain for a list of illustrations.

E. B. K.

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URINARY ANALYSIS AND DIAGNOSIS BY MICROSCOPICAL AND CHEMICAL EXAMINATION. By LOUIS HEITZMANN, M.D. Fourth edition. Pp. 362; 131 illustrations. New York: Wm. Wood and Company, 1921.

THE statement of the author of this book that he "makes no claims for completeness" in the 73 pages of the first part, which is devoted to the chemical examination, gives perhaps a sufficient indication to the prospective reader as to what he may expect therein. "As in the previous editions, the greatest stress has been laid upon the microscopic examination," which occupies 234 of the 340 pages of text. While it is undoubtedly true that microscopic examination of the urine should be carried out more carefully than

is generally done and that much can be learned from the higher powers of the microscope, the reviewer does not agree that "low magnifying powers . . . are decidedly useless" or that the microscope is preferable to other urological diagnostic methods as frequently as the author contends. Also, while there can be no question as to the value of many illustrations in a work of this kind, the diagrammatic quality of those here offered detracts greatly from their value to the urinalysist. Not only are many of the constituents unrecognizable without the identifying initials at the side, but also their stereotyped arrangement gives an unnatural bizarre effect recalling the advertising charts of enterprising manufacturers. The careful thought devoted to the details of microscopic examination, however, offers many valuable observations. E. B. K.

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A TEXT-BOOK OF MIDWIFERY. By KEDARNATH DAS, C.I.E., M.D., Professor of Midwifery and Gynecology, Carmichael Medical College. Pp. 477; 288 illustrations. Calcutta and Simla: Thacker Spink & Co., 1921.

THIS manual of midwifery is an abridgement of the larger handbook of Obstetrics, by the same author, which the reviewer had the pleasure of looking over some years ago. This smaller volume is offered to present the essentials of obstetrics to the Hindu students for whom it is intended. The outline of the text follows that of the previous volume, while in the condensation of the subject all noteworthy advances in obstetrics have been noticed.

But few criticisms may be offered. The subject of pituitrin is rather loosely handled, and while funnel-shaped pelves are described no mention of outlet measurements is found in pelvimetry. On the whole the book is a very good manual of the subject, concise, definite and up to date. P. F. W.

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HEART DISEASE AND PREGNANCY. By SIR JAMES MACKENZIE, M.D., LL.D., F.R.S., F.R.C.P.I., Hon. Consulting Physician to His Majesty The King in Scotland, Director of the Institute for Clinical Research, St. Andrews. Pp. 132; 21 illustrations. London: Henry Frowde, Hodder and Stoughton, 1921.

IN reading this book one is immediately impressed by the clarity and conciseness of the subject-matter, by the manner in which cardiac physiology is so simply yet thoroughly presented, and by the note of optimism in regard to the possibilities of reproduction in women suffering from heart disease.

The first part of the book discusses the normal changes in the circulation during pregnancy, labor and the puerperium, and the changes in the diseased heart during pregnancy. Then follows a description of heart physiology and heart disease in a general sense. After this come chapters on the lesions of the valves and on abnormal mechanisms of the heart's action, in which the complicating presence of pregnancy is taken up for discussion in an engaging personal manner, with usually an illustrative case, and with a short final summary to each chapter. The closing sections are on the management of cases of pregnancy associated with heart disease, and a final general summary, an excellent epitome of the subject.

Undoubtedly a study of this book, presenting, as it does, the latest word in cardiology, will assist the obstetrician in understanding more fully and treating with greater success heart disease during pregnancy.

P. F. W.

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OBSTETRICS AND GYNECOLOGY. Edited by JOHN S. FAIRBAIRN, M.A., B.M., B.Ch., F.R.C.P., F.R.C.S., Obstetric Physician, St. Thomas's Hospital. Pp. 950; 175 illustrations. London: Henry Frowde, Hodder and Stoughton, 1921.

APPRECIATING that reproduction, diseases of women and other medical and social aspects of woman's life are intimately intermingled, and with the conviction that such problems should be studied and taught under one head as they are met in practice, the editor has assembled these kindred topics in one volume. To this end the assistance of fifty-eight contributing authors, including five women, has been called upon to produce an unusually comprehensive, virtually encyclopedic, consideration of the reproductive system in woman and its correlated organs.

The volume is larger than most text-books, slightly difficult to handle from its bulkiness, and although the pages are double-columned the print is easily readable. The illustrations, while relatively few, have been well chosen. The subject-matter is divided in seven parts, composed of 109 sections or chapters. In order are discussed the female reproductive organs, normal and abnormal reproduction, the infant, diseases of women, public health, social and medicolegal problems and operative and other therapeutic procedures. It is interesting to note that puerperal infections are not discussed under the abnormal puerperium, but later as a gynecologic topic. The classification of morbid conditions in diseases of women follows a pathological rather than an anatomical basis. With so many authors some repetition has been unavoidable, but the difference in viewpoint is of value to the reader. The most marked example of reduplication is in the sections on the relief of pain in labor, and amnesic narcosis (twilight sleep).

It is difficult to single out any special part or section for commendation among so many excellent contributions. The modern trend of affairs is sufficient reason for the inclusion of the interesting chapters dealing with communal, social and legal aspects of woman's reproductive life. The volume is a splendid work of reference on obstetrics, gynecology and closely allied subjects, and reflects great credit on the editor and his large and very able staff of associates.

P. F. W.

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COLLECTED STUDIES OF THE BUREAU OF LABORATORIES OF THE CITY OF NEW YORK. DR. WILLIAM H. PARK, Director. Vol. IX, 1916-1919. Pp. 491. Published by the Department of Health of New York, 1921.

THE 58 articles comprising this volume (the first to appear since 1915) represent the investigations conducted under Dr. Park's direction between 1916 and 1919 by Krumwiede, Tingler, Hess, Pratt and other well known investigators in the New York Department of Health Laboratories. Although unfortunate that it could not either have been made to include more recent work or else have appeared earlier, it is like most collections of this kind an extremely useful reference book for workers in the same fields. The table of contents is classified into: (1) Applied Therapy and Preventive Medicine; (2) Bacteriology; (3) Chemistry; (4) Diagnosis; (5) Etiology; (6) Immunity; (7) Sanitation; (8) Physiology; (9) Serology.

E. B. K.

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THE HEART: OLD AND NEW VIEWS. By H. L. FLINT, M.D., Late Captain R.A.M.C., Cardiologist, Center for the Northern Command. Pp. 177. New York: Paul B. Hoeber.

THIS little book is divided into two parts. The first is entitled "The Heart in Antiquity" and contains a brief account of views regarding the heart and its diseases from earliest Sumerian times to the latter part of the nineteenth century. The second is headed "The Development of Instruments and Instrumental Methods." For the most part the discussion is concerned with the polygraph, the electrocardiograph and the arrhythmias. A brief historical summary of the development of knowledge concerning the functions of heart muscle is included. A few pages only are devoted to the interpretation of physical signs, the diagnosis of heart disease, heart failure and treatment.

The book contains much of interest and value for the student or practitioner who wishes to acquaint himself with the great names

and the great achievements in the history of cardiology. The account of the work of Harvey and his predecessors is particularly well done. One could wish that not so much had been said concerning the abnormal cardiac rhythms and more about the influence of scientific progress in increasing the effectiveness of ordinary clinical methods in diagnosis, prognosis and treatment.

C. C. W.

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STUDIES IN DEFICIENCY DISEASE. ROBERT McCARRISON, M.D., D.Sc., HON. LL.D. Fellow of the Royal College of Physicians, London; Laureat de l'Académie de Médecine, Paris; Honorary Surgeon to the Viceroy of India; Lieutenant-Colonel, Indian Medical Service. Pp. 270; 82 illustrations. London: Henry Frowde and Hodder and Stoughton, 1921.

TUCKED away in the heart of the Himalaya Mountains twenty days' ride from the nearest railroad station, four days' ride from the nearest white person excepting the three white companions he had with him, McCarrison, in the face of these obvious difficulties, has been able to carry out a splendid piece of scientific research work. When one thinks of the many obstacles that had to be met in the nine years of intensive study that this work represents one would not be surprised if it lacked certain details, was incomplete, or was not sufficiently well worked out, but in going over the text one is surprised at the very great completeness of the work and the minuteness with which the studies are conducted from every point of view. McCarrison has studied the effect of deficiency in food on different types of animals, notably the pigeon and the monkey. He has deprived large numbers of them of the various vitamins and then he has studied not only the effect this has had, in a general way, on the animals but he has also studied very carefully and closely the gross morbid and microscopical pathology of the various organs of these animals. It is this phase of his work which is particularly interesting. He shows, for example, that there takes place an enlargement of the adrenal gland as the result of any type of food deficiency, whereas the other endocrine structures tend to atrophy. He shows by very careful weighing of the different endocrine organs just how great is the change in size of these organs on deficient diets and shows microscopically also the changes that take place. The same plan is followed with the gastro-intestinal tract and with the heart and blood-vascular system, as well as the nervous system. In addition to his experimental work McCarrison in the fourth part of his book deals with the practical application of his deficiency disease studies which he has made experimentally. In addition to the usual diseases which we classify as deficiency diseases: pellagra, beriberi, and so on probably the most interesting observation that

he has to make in connection with the practicability of his studies is the frequency with which deficiencies in the diet can produce gastro-intestinal disorders. This is certainly throwing a new light on some of these vague conditions of the alimentary tract with which we have to deal with in our ordinary civilized life, and which we have not been wont to consider the result of improper diet.

Dr. McCarrison's book is extremely interesting and very well written and will amply repay those who read it. It is not merely a dry recitation of a series of experiments but it is a vivid presentation of a large series of absorbing experiments which should appeal to medical men.

J. H. M., Jr.

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THE SPLEEN AND SOME OF ITS DISEASES. By SIR BERKELEY MOYNIHAN. Pp. 129; 13 illustrations. Philadelphia: W. B. Saunders Company, 1921.

SIR BERKELEY MOYNIHAN, in 1920, delivered the Bradshaw Lecture of the Royal College of Surgeons of England, choosing as the subject of his address the surgery of the spleen and the diseases associated with a disordered spleen. He has now published this lecture as a small volume of 129 pages. The book represents a correlation of the surgery of this organ, as would be expected, with a discussion of the diseases which are associated with changes in the spleen. The volume can in no way be called a monograph, it is not sufficiently complete to warrant such a term, nor does the author apparently wish it to be considered as such, as the title of the book indicates in speaking of *some* of the diseases of the spleen. It can be recommended, therefore, as an interesting summary of our knowledge in part of some diseases presenting splenic pathology such as pernicious anemia, leukemia, Banti's disease, hemolytic jaundice, and other less important diseases. The book will be of value to those who are interested in diseases of the spleen but it cannot be considered as a reference book for those who are interested in the more abstruse and deeper problems of splenic diseases and the functions of the spleen.

J. H. M., Jr.

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ORTHOPEDIC SURGERY OF INJURIES. BY VARIOUS AUTHORS. Edited by SIR ROBERT JONES, K.B.E., C.B., F.R.C.S., Director of Orthopedics, St. Thomas's Hospital; Consulting Orthopedic Surgeon, Royal Infirmary, Liverpool; Hon. Adviser to the Ministry of Pensions (Orthopedic Surgery). Pp. 1231; 474 illustrations. London: Oxford University Press, 1921.

THE advance of orthopedic surgery during the past war has been enormous, and it is, perhaps, the outstanding feature in surgical

science. In these two large volumes Sir Robert Jones and a group of leading American and British orthopedic surgeons have contributed a vast amount of information based upon experiences in the treatment of war injuries. The thirty-nine chapters are contributed by thirty-six authors, three of whom are Americans, thirty-two British and one Portuguese, ex-King Manuel of Portugal. The first volume opens with a foreword by Sir Thomas H. Goodwin. Following this is a preface by Sir Robert Jones, who defines the principles of orthopedic surgery and traces the development of the great orthopedic centers of England and Scotland. A notable biographical sketch of Hugh Owen Thomas is contributed by Dr. Arthur Keith. He delineates the impress of this great Liverpool surgeon upon modern orthopedic thought and practice. The chapters on the Prevention of Deformities, by Gray, and the Principles of Orthopedic Surgery as They Apply to the Military Need, by Goldthwait, should be of particular interest to the military surgeon. Trethowan's chapter on Simple Fractures of the Upper and Lower Limbs is excellent, but one notes the absence of a single illustration. Splinting of War Fractures, by Carlisle, is well illustrated and the Thomas splints and their uses are described. Hey Groves contributes an interesting and well illustrated chapter on Ununited Fractures. Sir Robert Jones's contributions are three chapters, Malunion of the Femur, Ankylosis and Stiff Joints, Flail Joints and their Treatment. These are written in Jones's characteristic vein, practical and to the point. In discussing arthroplasties, reference is made to the use of Horsley's wax, the composition of which he does not mention. We should like to know more about it. In the chapter on Chronic Osteomyelitis, by Elmslie, Bipp is recommended, a preparation which has not been so popular in this country as in England. Chapters on The Knee-joint, by S. Alwyn Smith, Disturbance of the Lumbar Spine and Pelvic Girdle, by F. C. Kidner, Orthopedic Surgery of the Hand and Wrist, Walter I. Baldwin, Treatment of Disabilities of Joints of the Upper Extremity above the Wrist, Naughton Dunn, The Ankle-joint and the Foot, David McCrae Aitken, Amputations, Elmslie, and The Organization and Equipment of Centers for the Limbless are other articles incorporated. In this volume one notes the absence of references to the contributions of Willems, the great Belgian surgeon, who has revolutionized our knowledge of the treatment of acute septic joint infections.

Volume II. Over 400 pages of this volume are devoted to the peripheral spinal nerves and their injuries. In the vast field of war surgery no section has claimed so many observers or proved so fascinating and instructive as that which deals with injuries to the peripheral nerves. Beginning with a comprehensive description of the anatomy of the peripheral nerves by Patterson, illustrated by diagrams and photographs, a splendid chapter on Diagnosis of Periph-

eral Nerve Injuries, by Stewart and Bristow, follows. The chapter on Operative Treatment, by Sir Harold Stiles, is beautifully illustrated in color, and is one of the most complete articles on the subject. Written by a master, it stands out as a distinct feature of this volume. As a guide to the surgeon who contemplates operating on peripheral nerves, this chapter should be of great practical value. A chapter by Bristow on The After-treatment of Peripheral Nerve Injuries considers splintage, heat, electrical stimulation, massage, remedial exercises and reëducation. Two chapters on End Results of Nerve Injuries, with statistics based upon a large number of cases, follows. They are exceedingly instructive, but they should be condensed, as there is a great deal of repetition. Other chapters in this volume are Transplantation of Tendons in Irreparable Nerve Injuries, Injuries to the Head and Spine, Functional and Reflex Movements in Their Relation to Orthopedic Surgery, Muscular Movements and Nerve Lesions, Splints and Plaster, Plain Metal Splints, Electricity, Massage, Gymnastic Exercises, Hydrotherapy, Roentgen Ray, Curative Workshops, The Organization and Administration of a Military Orthopedic Hospital. Although dealing with problems affecting war injuries, the application of principles to industrial traumata makes them of extreme value to the neurologist, the general surgeon and the orthopedic surgeon. These books are comprehensive in their scope, written in a clear style, and undoubtedly stand out as a great contribution to the surgical literature of the Great War, and while there is much valuable information contained in this work, it could be profitably condensed.

M. B. C.

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MODERN ITALIAN SURGERY. By PAOLA DE VECCHI, M.D., Corresponding Member of the Royal Academy of Medicine, Turin. Pp. 250; 15 illustrations. New York: Paul B. Hoeber, 1921.

To Italy, Americans have traveled to see art and ruins but never to visit their hospitals or to learn from the Italian medical teachers. The achievements of Italy in Medicine and Surgery during the last war have been so great that the world can no longer fail to recognize them. Mikulicz, Sauerbruch, Morelli, Bassini, Pizzoli, Cadivilla, Porro, Girrdano, Durante, Ceci and a host of others have blazoned their names on the tablets of fame. America has a large industrious and intelligent Italian population. Indeed, New York City alone contains a larger Italian city than any to be found within the borders of the Kingdom of Italy itself.

For economic, scientific and artistic reasons it is desirable to promote a closer relationship. It is with this hope in view that the author, who has spent his entire professional life in America has written this volume. It is not a scientific review by any means, but



is a brief recital of what has been done. In Italy in the last fifty years enormous strides have been taken and now the nation can look with much pride on its present up-to-date scientific institutions and profession.

A brief account of modern Italian surgery, of the men who are distinguished of the institutions and the surroundings is presented especially for the purpose of bringing together the physicians and surgeons of Italy and America.

Aside from the purely scientific contribution the book makes very pleasant, interesting and instructive reading from the standpoint of general information.

E. L. E.

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SURGICAL CLINICS OF NORTH AMERICA. Mayo Clinic No., Vol. I, No. 5, October, 1921. W. B. Saunders Company, Philadelphia.

THE character and worth of the work produced and reported by the members of the Mayo Clinic needs no introduction or recommendation to the readers of medical and surgical subjects. This number of the Clinics is made up entirely of contributions from that staff, twenty-three in number. Every article brings the reader something new and useful. It is pleasantly free from endless statistical and case history detail and on the other hand is sufficiently free to thoroughly present the subjects under discussion. It is thoroughly illustrated, having 161 in this number.

E. L. E.

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MANUAL OF SURGICAL ANATOMY. By CHARLES P. WHITTAKER, F.R.C.S., F.R.S.E., Demonstrator of Anatomy, Edinburgh, etc. Third edition. Pp. 429; 90 illustrations. William Hood & Co., New York. Edinburgh: E. S. Livingstone, 1921.

THIS the third edition since 1910 shows the popularity of this work, which is primarily written for the student. It is in no sense a text-book, but merely an outline to be filled in by its study of larger works, attendance on lectures and work in the dissecting room. The details of surface anatomy have been omitted for the sake of brevity. The illustrations are largely original. The book is of a handy size, having good print on first-class paper. The text is clear and concise and the style pleasing.

E. L. E.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

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**A Clinical Lecture on the Orthopedic Treatment of Poliomyelitis.**—FAIRBANK (*Brit. Med. Jour.*, April 9, 1921, p. 517) says that it is customary for purposes of treatment to divide the course of a case into three stages: the early acute stage, which lasts while there is pain and tenderness in the muscles; the second, a convalescent stage, during which the recovery of power is taking place, lasts to the end of the first year, sometimes to the end of the second year; and the third stage, which begins after the lapse of two years. Until this stage all reconstructive surgery is delayed. During the first stage the spinal cord is the seat of a hemorrhagic inflammation, which is gradually subsiding. The first essential of treatment is rest, both for the spinal cord and affected muscles. Steps should be taken to provide absolute rest for all of the affected muscles, for, without fixation, deformities are certain to occur. The neutral position is one in which, as far as possible, no one muscle or group of muscles around a joint is favored to the detriment of others. Thus the foot is put at a right angle, the knees are straight, the hips are straight and the spine flat. Massage should be carried out with extreme gentleness. Electricity is useless at this stage. The author gives a word of caution concerning the spinal muscles: a case in which the spinal muscles, though slightly affected at first, have recovered but still remain weak when the child first begins to sit up, is just the subject for scoliosis. The possible causes of scoliosis in poliomyelitis cases are: paralysis or weakness of the spinal muscles on one side, the abdominal muscles in one loin and of the intercostals on one side, of one psoas; secondly, general weakness of all the spinal and accessory muscles; thirdly, contracture of one hip; fourthly, shortness of one leg; and lastly paralysis of one shoulder. In a case treated well throughout, a muscle which is absolutely paralyzed after twelve months must be regarded as hopeless. The treatment during the second stage consists

in keeping the part warm, relaxation of the paralyzed or weak muscles, massage and reëducation of muscles, to which must be added "correction of deformity." Additional covering for a paralyzed limb is essential even in summer months. Splinting is the most important factor of treatment. The splints must be left on day and night and removed only for washing and massage. As soon as recovery has progressed sufficiently, walking should be encouraged, suitable apparatus being employed. Reëducation of muscles means nothing more than exercises carried out with a minute regard for the development of individual muscles. Normal voluntary contraction is to be preferred. There is no doubt that active exercises are the best means of increasing the power of a weak muscle provided that muscle has recovered sufficiently to contract voluntarily. The causes of deformity are gravity and the inability of a weak or paralyzed group of muscles to elongate their opponents after the latter have contracted. Contracture in a muscle is proof of some though perhaps not very obvious recovery of tone in that muscle. The operative procedures are practically limited to tenotomies, fasciotomies, wrenching and tendon lengthenings. The latter is preferable in the bigger tendons. A not uncommon deformity at the knee, due to the pull of the biceps muscle, which has alone recovered or has recovered to a greater extent than the rest of the muscles about the joint, is a triple one—a combination of genu valgum, flexion of the knee and external rotation of the tibia. In all cases correction must be gradual. Osteotomy is not required. Tendon transplantation should never be done until at least two years have elapsed and never while any deformity present has not been fully overcorrected. Transplantation of a muscle which is only just acting is worse than useless. The transplanted tendon should always be attached subperiosteally rather than simply sewn to another tendon. Good results are not usually obtained by trying to make a pure flexor into an extensor. Arthrodesis should never be performed before nine years of age and gives better results if even farther delayed. In the shoulder there are two necessary conditions—fair power in the muscles fixing and moving the scapula, and sufficient recovery in the forearm and hand—to warrant the operation. Arthrodesis of the hip-joint and knee-joint in poliomyelitis seems to the author to be very rarely justifiable. In the ankle arthrodesis gives an excellent result in some cases. The result apparently depends on the stability of the subastragaloid and other joints of the foot.

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**Carcinoma of Large Bowel.**—SHETTON (*Brit. Med. Jour.*, April 16, 1921, p. 555) says that abdominal pain with irregularity of the bowels which is persistent for more than twelve months should be looked upon as sufficient to justify an exploratory operation, for good results can only be obtained when cases come sufficiently early. The author favors radical operations. The excision should be a free one—at least four inches of healthy bowel should be removed on each side of the growth, with the mesentery and lymphatic glands. End-to-end junction is advocated, with preference for simple suture of linen thread to any mechanical devices. Five cases which were operated within the brief space of eighteen days are outlined with good immediate results in 4 cases: 4 of the cases were of the columnar type and only 1 of the

sclerosing type; 3 of the growths occurred in the cecum, 1 in hepatic flexure, the other in the pelvic colon. In the author's experience the last-named region is the commonest site; moreover, the growth is usually of the sclerosing variety. The operation is a serious one and its mortality rate is high, but the alternative is either death or an artificial anus. The patient, however, in vast majority of instances, will accept the operation which will remove their disease no matter what the risk is.

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**Fracture of Skull in Children.** — MOORHEAD and WHEELER (*Ann. Surg.*, 1921, lxxiii, 72) say that a combination of vault and basal injury can be expected in a very large percentage in which the injury has been severe and when the violence has not been direct and localized in character; in the latter, vault fracture is more usual. The mortality of this series was 26 per cent, in which 5 per cent followed vault fracture, 10 per cent basal, and 11 per cent combined vault and basal injury; stated in another way, involvement of the base gave a mortality of 21 per cent, four times that of the vault. If associated injuries are excluded their mortality is only 17 per cent. Early death (within forty-eight hours) was due to the head injury or associated injury; thereafter, infection in the form of meningitis, often pneumococcic, was the chief factor: 16 of their cases died within twenty-four hours; this means that over three-fourths of the fatalities occurred within the first two days. By comparison with adults, children have 25 per cent better chance for life with an equal grade of skull injury. The number of cases requiring operation is relatively small. In this group 12 per cent were operated upon.

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**Surgery of Cysts of the Spleen.** — FOWLER (*Ann. Surg.*, 1921, lxxxiii, 20) says that there are 2 authentic cases of dermoid cysts recorded. These present studies include 90 cases of non-parasitic cysts of the spleen. Non-parasitic cysts are most common in women during the childbearing period; however, pregnancy and such antecedent diseases of the spleen as malaria and syphilis cannot be evoked for more than minor contributing roles. In the case of pseudocysts; trauma plays the most important role in the simple, large, unilocular, so-called hemorrhagic or serous type; the latter usually develops secondarily from the former. The influence of twisted pedicle, embolism and diseases of intrasplenic bloodvessels cannot be denied. In the case of true multiple cysts, inclusions of misplaced cellular nests (endothelium of the peritoneum or cells of origin of lymphatic spaces or vessels) during the developmental period, or as a result in later life of traumatic or spontaneous rupture of the capsule, or of perisplenitis, may result in multiple cysts of the serous or lymphatic variety. True neoformative cysts (lymphangioma, hemangioma) are not common. Sixty cases of non-parasitic cysts have been treated surgically, 11 by puncture, 14 by incision and drainage, 6 by excision or partial splenectomy, 30 by splenectomy. The latter is usually the method of choice. The mortality for splenectomy is 3.5 per cent. Echinococcus disease of the spleen represents the one type of parasitic cysts reported in the literature. This disease is rarely a surgical problem of the spleen alone, for in about four-fifths of the cases the liver or other organ is involved. There are about 100 cases recorded up to 1890. The mortality for 23 cases subjected to splenectomy is about 17 per cent.

**A Comparative Study of the End-results of Cholecystostomy and Cholecystectomy.**—MOORE (*Surg., Gynec. and Obst.*, 1921, lxxiii, 41) says that, in general, cholecystectomy is the operation of choice in all cases except where general debility or serious complications—such as abscess, peritonitis or previous extensive adhesions—make removal too dangerous or prolonged an operation. In such cases cholecystostomy with possible later cholecystectomy may be done with advantage. Judgment in selection of cases for removal, early diagnosis and early operation all make for the choice and ultimately vastly more satisfactory results of cholecystectomy. The value of this method of treatment for appendicitis is unquestioned, and it seems as logical to follow this same procedure in the case of a similarly affected gall-bladder. Moreover, the diseased gall-bladder has also come much into the limelight in recent years as a focus of infection in various forms of arthritis, anemias and general constitutional disturbances, and many of the removals have been followed by marked improvement in general bodily metabolism and welfare.

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**Reconstruction of Neck of Femur.**—WHITMAN (*Surg., Gynec. and Obst.*, 1921, xxxii, 479) says that ununited fracture of the neck of the femur is in most instances a painful as well as a crippling condition, for which operative treatment would be advised and accepted, in vigorous subjects, if definite relief could be assured. Technic of operation and cases cited. The reconstruction operation has a great advantage over bone-grafting in cases of the ordinary type, for the removal of the trochanter restores a bearing surface for the femur by reconstructing a neck which, when remolded, may be adjusted to the acetabulum to form a stable articulation. The displacement of the trochanter to a lower attachment on the femur in the attitude of abduction provides a muscular sling whose tension supports the limb in its proper rotation to the pelvis, while its outward projection restores effective leverage for the attached muscles, of which the glutei, the direct abductors of the limb, are the most important. The author would have all cases primarily treated by the immediate and efficient Whitman abduction method, which will be followed by repair in most instances. If union fails when accurate apposition of the fractured surfaces has been maintained for a sufficient time, as confirmed by x-ray examination, it indicates a low vitality of the tissues and, therefore, the advisability of the reconstruction operation in preference to bone-grafting.

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**Habitual or Recurrent Dislocation of Shoulder.**—HENDERSON (*Surg. Gynec. and Obst.*, 1921, xxxiii, 1) says that capsulorrhaphy to strengthen the shoulder gave 50 per cent cures in the 16 cases of habitual or recurrent dislocation of the shoulder. Five of the patients (31.25 per cent) are so decidedly improved that they are more than satisfied with the operation. This percentage of improvement and the percentage of cures give good results in 81.25 per cent. It is probable that muscle pull, or possible relaxation of the shoulder capsule above, has not been sufficiently considered in the treatment. It is reasonable to suggest, therefore, that the pectoralis major, teres major and latissimus dorsi be lengthened, and, if thought necessary, the region of the capsule where the supraspinatus and infraspinatus are inserted and the anterior inferior portion of the capsule be reefed.

## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

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**Quinidin for Relief of Auricular Fibrillation.**—In 12 of the 35 cases of auricular fibrillation treated by BOCK (*Deutsch. med. Wchnschr.*, 1921, xlvii, 1052) there was relief from the use of quinidin. The effect is usually transient; in some cases, however, the action is prolonged with no recurrence for from two months to a year. In some cases evident decompensation was relieved by quinidin. In absolute arrhythmia the author recommends quinidin and considers it especially valuable in persons with peripheral arteriosclerosis and hypertension. It is not suitable for the treatment of a case of acute and recurrent endocarditis.

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**Lobelia as a Respiratory Depressant.**—In depression of the respiratory center HOECHSTENBACH (*Deutsch. med. Wchnschr.*, 1921, xlvii, 876) uses lobelia hydrast. crist. Ingelheim intramuscularly or subcutaneously, as it acts as a direct stimulant to the respiratory center. In an emergency it may be given intravenously. It has a relaxing effect on the bronchi and is especially effective as an antiasthmatic.

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**Effect of Pituitrin on Specific Gravity of the Urine.**—*Deutsch. med. Wchnschr.*, 1921, xlvii, 869) found that pituitrin in normal individuals leads to the excretion of a more highly concentrated urine than normal, so that the specific gravity is at least 1.020 to 1.022. Where the kidneys are diseased pituitrin does not bring out this increased concentration. The pituitrin effect usually lasts for several hours after subcutaneous injection.

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**Calcium Solution as a Coagulation Accelerator.**—GOETTING (*Deutsch. med. Wchnschr.*, 1921, xlvii, 955) uses 10 cc of 10 per cent calcium in 3 per cent gum arabic solution intravenously. In three hours the coagulation time is cut in half and gradually returns to normal in twenty-four hours. This method was used in all types of hemorrhage, especially in hemoptysis and uterine bleeding, with uniformly good results. The injection was repeated on the following day in a few cases, but the second dose was given only as a prophylactic measure.

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**Adrenalin Intramuscularly and Subcutaneously Injected.**—CSÉPAI (*Deutsch. med. Wchnschr.*, 1921, xlvii, 953) found that if adrenalin did not act after subcutaneous injection it did not act after intramuscular injection with doses of 0.5 to 1 mg., or only very slightly. If, however,

it was given intravenously in doses of 0.02 to 0.03 mg. a blood-pressure rise was always established. There were great variations in the reactions from subcutaneous and intramuscular injection of adrenalin, but in no case did he fail to get a rise in blood-pressure from intravenous administration, regardless of whether or not reactions were obtained by the other modes of administration.

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**Salvarsan in Malaria.**—GLASER (*Deutsch. med. Wchnschr.*, 1921, xlvii, 867) reports the case of a syphilitic, aged twenty-eight years, who knew nothing about his latent malarial infection and who went through a course of salvarsan which provoked such a serious attack of "tropical malaria" that within fourteen days he was dead. In war veterans with unexplained postsalvarsan febrile symptoms one should always think of malaria. In ordinary forms of malaria salvarsan is curative, but in "tropical malaria" it does not sterilize the blood and in doses of 0.4 to 0.6 gm. stimulates the tropical malaria parasite. It seems to cause a sweeping of the organism into the blood stream.

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## PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

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**Experimental Studies on Hydrocephalus.**—NANAGAS (*Bull. Johns Hopkins Hosp.*, December, 1921) says that the pressure of cerebrospinal fluid in kittens in which an internal hydrocephalus had been experimentally produced was considerably higher than that of normal kittens. An average difference of 50 per cent was found in his series of observations. The maximal recorded cerebrospinal-fluid pressure obtained in this series was 171 mm.; the average of all cases was 126 mm., and the lowest was 100 mm. The average pressure of normal kittens was 76 mm.; the highest was 102 mm., and the minimal was 66 mm. Intravenous injections of a strongly hypertonic solution of sodium chloride in hydrocephalic animals produced a brief initial rise in the pressure of the intraventricular pressure of the cerebrospinal fluid, which was followed immediately by a marked depression. This decrease in pressure at times produced negative values. This phenomenon is probably to be explained by the apparently rapid absorption of the cerebrospinal fluid from the dilated cerebral ventricles. Intravenous injections of hypotonic solutions, such as distilled water, in hydrocephalic kittens was invariably followed by a marked and sustained increase in the pressure of the cerebrospinal fluid. This result was probably due to a rapid elaboration of fluid by the choroid plexus, or to an increased transudation of fluid through the ventricular walls. Intraventricular absorption of cerebrospinal fluid took place in these hydrocephalic kittens, and the pathway of absorption was

through the ependyma into the underlying capillary network. This absorption of cerebrospinal fluid was hastened by the intravenous injection of strongly hypertonic solutions. Absorption of the cerebrospinal fluid was similarly found taking place through the ventricular ependyma in normal kittens. The pathway of escape was the same as described above. The process of absorption was slow in the normal animals, but it was hastened by the administration of hypertonic solutions. The physiological significance of this intraventricular absorption in the normal animals is probably minimal. The choroid plexus took absolutely no part in the intraventricular absorption of the cerebrospinal fluid.

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**The Nature of the Plantar Reflex in Early Life and the Causes of its Variation.**—FELDMAN (*Am. Jour. Dis. Children*, January, 1922) studied 500 subjects from birth to seven years of age, most of whom were younger than four years. He obtained plantar response in 426 cases. He found that the prevailing plantar response in early life is plantar flexion of the big toe, although when a dorsiflexion of the toe occurred it was not of the same significance as the similar response in the adult. The pyramidal tracts are sufficiently developed at birth at full term to give an adult normal type of plantar reflex even intra-uterinely. Owing to easily aroused circulatory disturbances in early life the consequent changes in the circulation in the region of the cord are sufficient to compress the incompletely myelinated pyramidal tracts to evoke a Babinski phenomenon either unilaterally or bilaterally. In premature infants the response is nearly always of the Babinski type, up to five or six weeks of postnatal life, because of the almost total absence of myelization of the pyramidal tracts. Malnutrition, as judged by defective weight and length, go hand-in-hand up to about five or six weeks. The Babinski sign seen in badly developed infants up to that age is due to prematurity rather than to the malnutrition. Bilateral plantar flexion is at all ages as common in girls as in boys, but bilateral dorsiflexion is at all age periods in infancy more common in girls. Breast-feeding during the first four weeks of life probably tends to diminish the incidence of the Babinski phenomenon. This may be due to the greater percentage of lecithin and lactose in human milk, which helps the more rapid myelization of the pyramidal tracts. After the first month or so breast-feeding has no advantage in this respect over bottle-feeding. Toxic influences, either from the bowel or other causes, do not affect the conductivity of impulses along the fibers of the pyramidal tracts. Bilateral dorsiflexion is slightly more common in dolichocephalic than in brachiocephalic infants, possibly because inhibitory control is less powerful in the former than in the latter. Rickets does not favor the occurrence of the Babinski reflex. The age at which the sign vanishes has no relation to the age at which the child begins to walk. In the majority of the cases of very young infants who could not even sit up the Babinski sign was absent, and in the large number of cases of the children who could walk the Babinski sign was present. As the peripheral nerves are imperfectly myelinated at birth a possible explanation of the Babinski phenomenon in certain infants is the more imperfect development of the lower motor neuron supplying the flexors of the toes, and better development of the neuron



supplying the extensors. The inconstant nature of the response in certain infants in whom there may be obtained, at the same examination, on one stimulation a plantar flexion, and on another stimulation a dorsiflexion, may be due to the easy fatiguing as well as the easy recovery from fatigue of young muscle, so that after a certain response has been obtained the muscles producing that response can no longer contract as readily as the opposing group of muscles. The response is therefore produced by the less-fatigued group of muscles. The reflexogenous zone is very diffuse in early infancy, and sometimes a cutaneous area other than the surface of the sole gives the plantar reflex when stimulation of the sole fails to evoke a response.

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**The Incidence of Protein Sensitization.—In The Normal Child.**—PESHKIN and ROST (*Am. Jour. Dis. Children*, January, 1922) found that 10 per cent of the children showed doubtful and positive reactions, which decreased as their age increased, indicating progressive desensitization. The incidence of sensitization in normal as compared with abnormal children indicated that the ratios were similar to the tabulations of Walker in 400 cases of bronchial asthma, where it was noted that four-fifths of the patients whose asthma began in infancy were sensitive; two-thirds whose asthma began in childhood were sensitive; one-half of those whose asthma began during young adult life were sensitive; one-quarter whose asthma began during adult life were sensitive; and none were sensitive whose asthma began after middle life. The foods giving doubtful and positive reactions were those frequently indulged in and composed the essential part of the dietary. The foods giving the greatest number of reactions in these normal children corresponded proportionately with those in the abnormal children. It was found that the administration of diphtheria antitoxin incurred practically no risk of anaphylaxis.

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**Bacteriologic Studies of 165 Cases of Pneumonic and Postpneumonic Empyema in Infants and Children.**—LYON (*Am. Jour. Dis. Children*, January, 1922) studied in this series 98 cases of lobar pneumonia, 52 cases of bronchopneumonia and 15 cases of postpneumonic empyema in children and infants twelve years of age or younger. In lobar pneumonia or in empyema following lobar pneumonia the pneumococcus of Type I was found in 29.9 per cent; pneumococcus of Type II in 3 per cent; pneumococcus of Type III, 7.1 per cent; and pneumococcus of Type IV in 37.7 per cent. The general reliability of these findings is suggested by the reasonably close correspondence to the findings in a parallel series of cases in adults. Studies of comparative mortality suggest that the child possesses better natural immunity against the pneumococcus, type for type, than does the average adult. In bronchopneumonia the fixed types of pneumococcus were much less common than in lobar pneumonia. Common mouth forms were relatively much more common. Regardless of type the general mortality of bronchopneumonia is much greater than for lobar pneumonia. This is probably due to the conditions, origin and circumstances surrounding the disease. Streptococcus hemolyticus and Staphylococcus aureus were more common in bronchopneumonia and were followed by a particularly high mortality. There was an

extraordinary tendency to the development of empyema in infections with pneumococcus of Type I. Almost 38 per cent with this type of infection developed this complication, and this was six times greater than any other cause of empyema.

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**Mongolian Idiocy in One of Twins.**—McCLEAN (*Jour. Am. Med. Assn.*, January 7, 1922) reports an instance. He says that since the original description of Mongolian idiocy by Down and the more complete description by Kassowitz there has been but small addition to the knowledge of this condition. The etiology is unknown. Attempts have been made to assign syphilis as a cause, but reports of positive Wassermann reactions in certain Mongolian idiots have never misled the careful clinician. The extremes of age in either parents have also been considered, but Goddard in an analysis of more than 290 cases found that the ages of fathers of Mongolians varied from twenty to sixty-three years. He found that the number of Mongolians born of mothers of forty years was much higher than at any other age. In 30 cases reviewed by von Hofe the mother was less than thirty-five years of age in 47 per cent. Consequently any influence of the age of either parent seems to have no foundation of fact. Goddard inclines to the belief of many others that the condition of the mother during pregnancy has a strong influence upon the development of this condition. If this is true the same changes are to be expected in both twins. Such a result was seen in the cases of Hjorth. Seven other cases similar to this one have been found in the literature. Instances of more than one case of Mongolian idiocy in the same family have been reported, the most recent being that of Pardee, who suggests the endocrine disturbance as the probable cause. If there was an endocrine disturbance in the mother in the case here reported, which might manifest itself in a Mongolian offspring, it would naturally be expected that the other twin be similarly afflicted. The author suggests the following explanation: Two ova were fertilized by two spermatozoa; one of the ova was fertilized by a normal spermatozoön and resulted in the normal child; the other ovum may have been abnormal and have been fertilized by a normal spermatozoön, or may have been normal and fertilized by an abnormal spermatozoön. This fertilization resulted in the Mongolian idiot.

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**The Cure of Infantile Rickets by Sunlight.**—HESS and GUTMAN (*Jour. Am. Med. Assn.*, January 7, 1922) treated their patients by direct sunlight for from one-half to several hours, the period varying according to the sun's intensity, weather conditions and the condition of the baby. They point out that the important factor is the use of the direct rays of the sun without any interference by clothing or window-glass. The explanation of this is that the curative rays seem to be filtered out by passage through other media. In a previous communication they pointed out that this treatment cannot be routine but must be varied according to the condition of the babies, some being far more sensitive to sunlight than others. It is important that the babies be kept warm. It was found sufficient to expose the legs and arms, although it is preferable when the temperature permits to expose the trunk as well. Prior to treatment the majority of this

series showed clinical symptoms of mild rickets, such as beading of the ribs and the characteristic changes in the epiphyses as seen in roentgen-ray examination. They all received the customary milk mixtures as well as orange juice, and the older ones received cereals as well. In every case in which heliotherapy was used the rickets diminished and the general condition improved. The inorganic phosphate of the blood increased as it does also under the administration of cod-liver oil, which must be considered a specific for this condition. The experience of the authors did not justify any conclusions as regards the acid-soluble and the total phosphorus.

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**The Prevention of Rickets in Rats by Sunlight.**—POWERS, PARK, SHIPLEY, MCCOLLUM and SIMMONDS (*Jour. Am. Med. Assn.*, January 21, 1922) undertook this study to determine whether or not sunlight would prevent the development of rickets in rats. A diet was used which at room light regularly gave rise to a disease in its essential features identical with rickets of human beings. The diet was high in calcium, low in phosphorus and was insufficiently supplied with fat-soluble vitamine A. In other ways it was well constituted. Eighteen rats were placed on this diet. Twelve were exposed to sunlight for a total of two hundred and forty-two hours over a period of sixty-two days. Six were kept under conditions of ordinary room light as control animals. The control rats killed with ether at the end of sixty days all showed rickets. The rats exposed to sunlight remained without exception entirely free from rickets as confirmed by histologic examination. The beneficial effect of the rays of the sun was not limited to the skeleton, as the general condition of the animals underwent an improvement under the influence of the sunlight. The exposure to the sun's rays did not entirely compensate for the defects of the diet. Though the sunlight did not alter the defects in the diet, it permitted the animals to thrive to a limited extent in the presence of the diet. The sunlight somehow raises the efficiency of the body cells. The effects of sunlight and of cod-liver oil seemed to be identical.

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## OBSTETRICS

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**Experimental Studies in the Toxicity of Placental Lipoids and the Cause of Puerperal Eclampsia.**—SCHOENFELD (*Arch. f. Gynäk.*, 1921, cv, 80) contributes an interesting article to the literature already existing, indicating that substances in the placenta are active in causing eclampsia. He finds that extracts from the placenta made with alcohol, acetone or glycerin contain a poisonous material which produces

convulsions and is not soluble in ether or petroleum extract. This material (probably of the nature of a ferment) is only indirectly or partially soluble in alcohol. When an alcoholic extract is treated with ether, there remains a crystalline substance, little soluble in water and more soluble in glycerin, which produces convulsions when injected into animals. This substance loses its property of producing convulsions when it is heated to 70° C. for one hour. Lipoid and fatty substances are active poisons for parenchymatous organs and also for the endothelial lining of the bloodvessels. They seem to have an elective action on the cells of the liver and attack them more violently and rapidly than the cells of the kidneys. This action is especially seen in the nuclei. A process of degeneration develops, which ultimately destroys the nuclei, leaving the cells with cavities and fatty material. Ultimately the whole cell is destroyed. Where this substance is absorbed for a long time in quantities not sufficient to cause death, one can observe in the liver evidences of a process of attempted regeneration. Multinuclear cells form with abundant mitoses and finally cells with many nuclei and their regenerative bodies. In the kidneys the lesions occur in the cells of the bloodvessels. Thromboses are frequently found in the lungs, in the liver and sometimes in other portions of the body. This result follows the injection of extracts of the placenta made with alcohol, ether, chloroform or petroleum and ether. The lipoids of the placenta are typical cell poisons. The material obtained from the brain is probably not a lipoid as it is not soluble in ether, chloroform or benzine and but slightly soluble in alcohol, but is readily dissolved in glycerin and water. If the effort is made to isolate these materials, one can recognize practically the following: A substance producing convulsions and elevation of temperature, comparatively small in bulk, probably a ferment and which is easily dissolved or rendered available by glycerin; a substance which excites action of the uterus and which is little affected by heat and is a poisonous material, producing thromboses—probably lipoid in character; also a substance which affects the cells of the liver, the kidneys and the bloodvessels (which is probably a lipoid). When one comes to study the relation which these substances bear to eclampsia, one must observe that the lipoids, which are extracted from the placenta, seem to be secreted by the placenta itself. Various observers have found drops of lipoid and fat in the placenta and also in the syncytium. In pregnancy the blood contains abundant lipoids, which are much increased during the toxemia of pregnancy. It is especially interesting to know that in the preëclamptic and eclamptic condition the blood of the pregnant women is exceedingly rich in lipoids and in substances which are like cobra poison. An extract of the blood of pregnant animals, made with ether, is poisonous for animals which are not pregnant; the extract from the blood of animals not pregnant, made in the same way, is not poisonous. In chronic nephritis and in diabetes a similar condition is found and the source of these lipoids is not clearly known. There seems to be no relation between this condition and uremia or acidosis. It has been thought that the action of the liver is lessened in these cases, and that that is shown by the increase in the percentage of cholesterin. This increases toward the end of pregnancy, although there is some diminution in the quantity

of bile; one may readily understand that the accumulation of this material might be of importance. Researches in other departments of medicine go to show that in various diseased conditions, the lipid content of the blood is greatly changed. It is thought by many that lipoids in the blood are a distinct element in producing epileptic convulsions, and that convulsions occur when the plasma of the blood reaches a certain stage of concentration. If the lipoids thus contained produce convulsions, but act by poisoning the cells of various organs, the decomposition of these cells would readily account for the formation of lipoids. This substance is probably not cholesterol but probably another lipid. In the placenta lipoids are found more abundantly in the first six months than in the last three. In the blood the relationship is reversed. In cases of abortion produced by the toxemia of pregnancy an increase in fatty substances is often observed, which is not peculiar to pregnancy, but is often seen in the infectious diseases with or without fever. It is evident that the changes which precede eclampsia and toxemia are gradually developed and are not of sudden origin.

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**The Formation of Bone in the Skeleton of the Mother during Pregnancy.**—DREYFUSS (*Arch. f. Gynäk.*, 1921, cv, 126) has made extensive investigations regarding the question of the formation of osteophytes during pregnancy. He finds that by using the stereoscope with roentgen-rays one can demonstrate the changes in the wall of the skull in pregnancy very plainly. He finds that instead of an increase of 50 per cent.—as has been already computed, largely from the examinations of the skeleton of the cadaver—in the living an increase of  $33\frac{1}{3}$  per cent is what is really present.

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**A Case of Necrosis of the Intestine in the Ninth Month of Pregnancy.**—PILSKY (*Zentralbl. f. Gynäk.*, November, 1921, p. 1662) reports the case of a primipara, who up to two days before admission to the hospital, seemed to be in good general health. She was then taken with sudden pain in the region of the stomach, with vomiting. On the following day the pain grew better, but the prostration and vomiting continued. A midwife administered castor oil without improving the patient's condition. Since the beginning of her illness the patient had no bowel movement and passed no gas through the intestine. Severe abdominal pain again returned and labor pains developed which brought the patient to the hospital. On examination she was badly nourished, without edema or eruption; the tongue was moist and not coated. The abdomen was somewhat enlarged and there was diffuse tenderness over the whole abdomen; the pelvis was normal. The head of the child was in the pelvis; the heart sounds rather feebly heard. Labor went on and a poorly developed child (42 cm. long) was spontaneously born. The patient felt considerably better after labor, although she vomited freely of greenish fluid. This continued until the material vomited became blackish green and the abdomen was somewhat tender. The tongue did not look badly. The patient gave no sign of peritonitis. During the night the distention of the abdomen and tenderness increased and a high enema gave no result. The lower abdomen was very tender, especially in the region of the

large intestine, and a diagnosis was made of intussusception. At operation dark reddish fluid was found in the abdomen. The peritoneum was not clear and the condition of the intestine and omentum was abnormal. From the posterior wall of the uterus there were bands of adhesions of a grayish yellow color which bound down the intestine. On examination a considerable portion of the intestine was found necrotic, and it was necessary to resect a piece (35 cm. in length). The abdominal cavity was irrigated with warm salt solution and gauze drainage was inserted. The patient died some hours afterward, as the operation had been undertaken too late. It is probable that the pregnancy was at least the indirect cause of the abdominal condition. The growing uterus had forced the intestine up and occluded a portion of it and brought about the necrosis. The painful movements of the intestine had brought on the labor, and the labor had increased the difficulty by aggravating the inflammation of the bowel. Postpuerperal ileus develops because the intestine in pregnancy loses its tone and because in some cases labor is difficult and greatly prolonged. This is seen in contracted pelvis, hydramnios and in cases of pregnancy complicated by diseases of the heart or kidneys. Evidently if operation is to be done in these cases, it must be instituted very promptly.

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**Fibroids Complicating Pregnancy and Labor.**—MARSHALL (*Lancet*, December 10, 1921) states that in pregnancy complicated by fibroids the production of abortion is not indicated. The development and comparative safety of delivery by abdominal section makes this unnecessary. Many women having fibroids do not conceive, and in some cases women who had born children, subsequently became sterile because fibroids developed. With fibroids, submucous or polypoid, there was a tendency to abortion, but in even these cases the pregnancy might go on to term. All varieties of fibroids may bring on abortion. He describes the case of a woman in her second pregnancy who had a large subserous fibroid projecting from the anterior uterine wall at the level of the umbilicus. There was slight hemorrhage and labor gradually came on, the child being delivered without difficulty. At each uterine contraction the fibroid became hard and protruded and this gave the patient severe pain. Pregnancy complicated by fibroids may be divided into those cases which might safely go to term, those in which myomectomy can be done and those which require hysterectomy. Abortion should not be performed. Large tumors sometimes will rise out of the pelvis as the uterus grows and thus give room for the normal birth of the child. In those cases where the patient might go to term the main complications which are to be feared are pain and hemorrhage. These patients should first be treated by rest, sedatives and general treatment. Where a subserous fibroid became twisted and necrosis developed the indications for operation were clear. This was also true in prolapse and impaction of a subserous fibroid in the pelvis or a fibroid on the anterior uterine wall causing retroflexion likely to end in abortion, great pain or incarceration. The subserous type of tumor was best adapted for operation. Where pregnancy was complicated by an interstitial fibroid of any size it was best not to attempt its removal because of the hemorrhage,

the weakening of the uterine wall and the frequency of abortion afterward. He had operated in 3 such cases; 2 going to term, and the third later on had aborted. Where the tumors were such that operation was indicated, the patient generally suffered from considerable pain. The majority of cases which went to term ended in spontaneous labor, but very often there were complications in very severe pain, inertia of the uterus, abnormal presentations and sometimes rupture of the uterus. Where a fibroid is in Douglas's pouch, it can sometimes be pushed above the brim to permit delivery. Where labor is obstructed by fibroids Cesarean section is indicated. If the tumor is so situated that labor can readily go on, the tumor may be removed at some time after labor or if the fibroids were extensive and if there was possible infection, hysterectomy should be done. Craniotomy should not be performed, and nothing could be worse than pulling the head of the child past an obstructing fibroid tumor with forceps. Postpartum hemorrhage (both primary and secondary) is often seen after labor in cases complicated by fibroid, and septic infection is not infrequent. If there was severe pressure or injury during labor the tumor might undergo degeneration, and septic infection develop. During a forceps delivery the tumor might be injured and infection develop later. After a pregnancy fibroid tumors sometimes shrink to a very extraordinary degree.

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## GYNECOLOGY

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**Postperitoneal Tumors.**—In reporting a case of postperitoneal cystoma, GRAVES (*Surg. Clinics of North America*, June, 1921, p. 607) discusses the histogenesis of postperitoneal tumors in general. They appear in a great variety of forms including fibroma, fibrosarcoma, lipoma, simple serous cystoma, multilocular serous cystadenoma, teratoma, dermoid cystoma, etc. One may readily imagine that such tumors as the fibromata and lipomata have their origin in the subperitoneal cellular tissue in a manner entirely analogous to that which they exhibit in any other part of the body. The unusually large size that they may attain postperitoneally is doubtless due to the slight tissue resistance that they encounter during their growth. One may also imagine that some of the simple serous cysts may arise from isolated rests of the Wolffian ducts. The histogenesis of certain of these growths is, however, not so easily explained. Especially is this true of the dermoids and teratomata. These tumors, whether they originate in the ovaries

or postperitoneally, are unquestionably ovigenous. Their development in the postperitoneal cellular tissue has been usually attributed to misplaced blastomeres that, after the original segmentation, have wandered away from their normal place of assembly in the genital gland and have become isolated at some point in the postperitoneal space. The acceptance of this explanation implies a belief in the germ-plasm theory of Weissmann, which asserts that the germ-cells (ova and spermatozoa) are entirely independent in their relation to the body or somatic cells, both in origin and growth. Recent studies in the embryological development of the germinal epithelium covering the ovary have done much to disprove this theory. Thus it has been shown that the genital gland originally develops from the germinal epithelium, which is itself a local modification of the peritoneum. The growth in size of the genital gland is due to an invasion downward of the germinal epithelium, and it has been shown that all the cellular elements of the ovary with the exception of a fine connective-tissue framework are derived from the down-growing germinal epithelium. These cellular structures include the stroma, interstitial cells, the remains of the rete ovarii, and cords of Pflueger, the granulosa layer of the Graafian follicles and finally the ova themselves. It may be seen, therefore, that the ovarian dermoids and teratomata, being ovigenous, are derived in the last analysis from the germinal epithelium. It has also been conclusively proved that the serous cystadenomata are derived directly from the germinal epithelial layer that invests the ovary. Bearing these facts in mind, Graves argues that if the embryonic peritoneum has the power of a local differentiation into the germinal epithelium, which in turn may produce germ-cells, it is entirely conceivable that this power of differentiation may abnormally appear in parts of the peritoneum other than in that portion which is eventually destined to become a genital gland. In this way cells may be created in different areas of the sub-peritoneal space exactly similar to those in the ovary which have the power of becoming dermoids or teratomata.

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**Construction of Artificial Vagina.**—The technic which GRAVES (*Surg. Clinics of North America*, 1921, p. 611) employs in the construction of an artificial vagina begins with a transverse incision, about two inches in length, which is made across the space usually occupied by the introitus. With blunt dissection a plane of cleavage is sought beginning just above the commissure of the levator ani muscles. It will be found that the tissues may be separated with comparative ease, but some bleeding is encountered, so that it is necessary to proceed cautiously with the separation. In this way an opening is made which corresponds in its proportions to a normal vagina. It is important not to enter the abdominal cavity. Several catgut sutures with long ends are placed in the vault of the new opening and the ends tucked into the pouch for later use, as will be described. The second part of the operation is to line the opening thus formed with skin turned in from the surrounding parts, which may be best accomplished in the following manner: The labia minora are first partially amputated, the incisions beginning near the clitoris and continued downward toward the artificial opening, but leaving sufficient pedicle to allow competent circulation. The skin layers of the partially amputated labia are then separated so that they



appear as two paddle-shaped flaps. Two similar flaps are then dissected from the thighs. A third and if need be a fourth may be taken from the buttocks. In outlining the skin flaps it is important to mark the pedicles of the paddle-shaped areas in a *curved* direction. By observing this rule the flaps may be turned face outward without causing disagreeable folds at their attachments near the artificial opening. The skin wounds made by the removal of the flaps having been sewed, a glass form, such as is used for maintaining a dilatation of the vagina, is placed at the artificial opening, but pointing *outward*, the five or six skin flaps are sewed together over the glass form, the flaps being turned so that the skin surfaces face externally. Great care should be taken to secure accurate coaptation of the skin edges and to fit the cap of skin smoothly over the glass form. When the sewing of the skin flaps has been completed the ends of the sutures that had been attached to the vault of the artificial pouch are now brought out, threaded into needles, and passed through the dome of the cap made up of skin flaps. By carefully inverting the cap the artificial pouch becomes lined with a layer of skin, which may be fastened snugly in place by tying the sutures that had been placed in the vault. The final step in the operation is to close with fine catgut sutures the remaining openings in the skin flaps at the introitus.

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**Indications for Radiotherapy in Cervical Cancer.**—In these days when so much is said in favor of radium and almost as much is said against its use, we are greatly interested in obtaining the opinions of level-headed men who are neither radium enthusiasts nor operative maniacs. It is therefore of interest as well as of much importance to the profession to note that GRAVES (*Surg. Clinics of North America*, 1921, p. 615) uses radium for the treatment of cervical cancer only in inoperable cases. It should also be noted, however, that since the advent of radium, his definition of what is operable and what is inoperable in cervical cancer has undergone some modification. Formerly he regarded as operable a case of cancer wherein it appeared possible to perform a radical operation without killing the patient or without mutilating the hollow organs of the pelvis, even though it seemed probable that a permanent cure of the disease could not be effected. This policy was pursued because such operations usually palliated the patient's symptoms and often greatly prolonged her life. Since the acquisition of radium he has come to define as operable only those cases in which a radical operation offers some chance of obtaining a permanent cure. This viewpoint has been reached because he has found that in these sub-borderline cases radium sometimes, though not always, produces palliative results equal to those of radical operation, and does not subject the patient to operative risk. He has not yet become convinced that in an operable case (or perhaps one should say a *curable* case) we are giving the patient as good a chance for ultimate cure by radium as we are by operation. Graves has only 100 mm. of radium, and although this amount has been of inestimable benefit as a palliative agent it has not infrequently proved unreliable and treacherous, and therefore he is convinced that his equipment is too meager to warrant its use in a frankly operable case,

**Operation for Rectovaginal Fistula.**—Although not claiming originality for the procedure, HUBBARD (*Surg. Clinics of North America*, 1921, p. 867) describes an operation for the cure of rectovaginal fistula which seems to have considerable value in selected cases. It should be remembered that the condition causing a rectovaginal fistula almost necessarily leaves a woman with a badly torn perineum. Therefore this operation is planned not only to cure the fistula but also to repair the perineum. A curving incision is made at the line of junction of the mucous membrane of the vagina and skin and a flap of mucous membrane is turned up from the floor of the vagina until the fistulous tract made evident by a probe passed through it is reached. The tract is then dissected out intact, separated from the vaginal opening but not from the rectal opening. A hemostatic forceps is then passed through the fistula from the rectum, fastened to the vaginal end, then pulled back through the rectum, turning the fistula inside out. Should the fistulous tract be too small to admit even a mosquito hemostatic forceps it might be possible to accomplish the inversion by a suture passed from the vaginal end of the tract through the fistula and out of the rectum. A pull on this would invert the tract unless its lumen were too small to accommodate the thickness of even its own wall. By putting some tension on the fistulous tract thus turned inside out, the sides of the fistula, where it passes through the rectal wall, are brought together. The opening in the rectum is then closed on the perineal side by catgut sutures, which may be placed so that the knot is in the rectum or not. The excess of tissue containing the fistula is cut away, the opening in the vaginal mucous membrane is closed and the perineum is repaired by pulling the muscles on either side of the denuded area together by buried catgut sutures. This operation is naturally most easily done when the fistula is situated low down, but is applicable to one higher up, the limit being only determined by the accessibility. It has the distinct advantage of entire removal of the fistulous tract and separation of the suture line in the rectum from that in the vagina by considerable distance, by the aid of the plastic, which places the thick bellies of the perineal muscles between the two suture lines, thus materially decreasing the chance of recurrence.

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## PATHOLOGY AND BACTERIOLOGY

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**Experimental Typhoid—Paratyphoid Carriers.—II.** *The Optimum Hydrogen-ion Concentration for the Growth of Bacillus Typhosus and Bacillus Paratyphosus A and B.* Employing methyl red, bromthymol

blue, cresol red and thymol blue as indicators, SCHOENHOLZ and MEYER (*Jour. Infect. Dis.*, 1921, xxviii, 384) investigated various strains of typhoid and paratyphoid bacilli to determine the probable range of growth and the optimum H-ion concentration. Preliminary experiments were undertaken to arrive at the effect of varying concentrations of various chlorides and phosphates on *Bacillus typhosus* so that the phosphate concentration used in the "optimum growth" experiments could be kept below an inhibitory concentration. It was learned that *Bacillus typhosus* had a growth range from  $P_h + 5.0$  to  $P_h + 8.6$  with an optimum growth at  $P_h + 6.8$ — $P_h + 7.0$  in the salt-free veal infusion broth employed. Large variations in the H-ion concentration near the optimum zone produced only slight effects on the growth of the bacteria, whereas slight variations at the limiting zone had a marked effect. In the region near the optimum H-ion concentration the tolerance for alkali seemed to be slightly greater than for acid. Stock cultures recovered from stools, blood and urine of typhoid patients or carriers had a more decided optimum than recently isolated cultures of similar cases, the latter cultures having a more pronounced and wider range of growth than the former. This, the authors believed, was suggestive of microbic adaptation to changes in the H-ion concentration in body fluids, especially urine and bile. *Bacillus paratyphosus* A and B had a range of growth similar to *Bacillus typhosus* but exhibited a greater tolerance for alkali.

III. *Do "Carrier" Strains Differ from Strains Isolated from Ordinary Typhoid Cases?* In an attempt to elucidate certain facts recorded in the literature pertaining to animal carriers and not to attempt to prove or to refute the idea that the typhoid strains isolated from human carriers may differ in their invasive or infective properties, CHRISTIANSEN, NEILSON and MEYER (*Jour. Infect. Dis.*, 1921, xxviii, 394) immunized rabbits with fourteen different carrier strains by at least six intravenous injections, at six to seven day intervals, of heat-killed (53 to 54 C), tricrosolized, autogenous cultures on rabbit blood agar, in doses increasing from  $\frac{1}{20}$  to  $\frac{1}{2}$  of a slant. Ten to fifteen days after the last injection of vaccine, the animals received the same strain of *Bacillus typhosus* in the living state. All rabbits were free from coccidiosis and spontaneous cholecystitis. The rabbits were sacrificed in from twenty to twenty-five days after the inoculation. Cultures were made on endo-agar plates or by enrichment of portions of the organs in 10 per cent ox-bile rabbit broth. At this time, the authors regarded the presence of typhoid bacilli in the bile and gall-bladder wall as constituting a positive result. No striking differences were found between the fourteen carrier strains and those isolated from acute typhoid cases. Seven carrier strains tested on rabbits by means of intravenous injections failed to exhibit specific elective cholecysto- and renotropic properties. Furthermore, it was impossible to confer such characteristics to a recently isolated *Bacillus typhosus* strain by successive passage through rabbit gall-bladders. Immunized rabbits inoculated with large doses of living typhoid bacilli exhibited gall-bladder infections in a higher percentage of instances than normal rabbits.

IV. *A Comparative Study of the Infections Produced by Intravenous Injections of Typhoid, Paratyphoid A and B Bacilli in Normal and Immunized Rabbits.* "In order to establish a carrier state with absolute

regularity, it is unquestionably necessary to obtain as clear a picture as possible of the cycle of events which follows the intravenous injections of Gram-negative bacilli in the rabbit." MEYER, NEILSON and FEUSIER (*Jour. Infect. Dis.*, 1921, xxviii, 408) reported the results of experiments dealing with the fate and disappearance of typhoid and paratyphoid bacilli, at the same time contributing to the questions as to why the gall-bladder becomes infected and why it frequently retains the infection. The bacterial counts of the organs removed from the exsanguinated rabbits at varying periods of the injection were made by the plate dilution method. It was found that a small number of typhoid bacilli inoculated intravenously into normal rabbits of the same litter was rapidly removed from the blood stream at the end of from ten to fifteen minutes, that 20 to 30 per cent of the inoculum was found in the liver, a small amount in the spleen, bone marrow and lungs and comparatively few in the lymph nodes, kidneys, muscle, etc. The gall-bladder bile contained only a small number of bacteria, while the gall-bladder wall received according to its size a proportional share of the total number of the bacteria deposited in the liver. Large numbers of typhoid bacilli were less speedily removed from the blood stream, but the distribution in the organs remained the same in the first four to eight hours. The gall-bladder was capable of being infected either as a result of an immediate extensive elimination of the introduced bacteria or through the continuous discharge of bacilli from liver foci in the hepatic bile or in consequence of an embolic infarction of the gall-bladder capillaries. In the latter instances the cystic bile would not become invaded with *Bacillus typhosus* for twenty-four to forty-eight hours after the intravenous injection. It was further learned that the distribution and destruction of small or large doses of typhoid bacilli was practically the same in the normal as in the immunized rabbit, whether protected by the injection of dead or viable organisms. Animals which died of typhoid intoxication regularly harbored many typhoid bacilli in the marrow of the long bones, so that these foci were probably the seed beds responsible for the continuous invasion of the blood stream and the later overwhelming infection of liver and spleen. Paratyphoid A bacilli acted in a manner identical to *Bacillus typhosus*, but *Bacillus paratyphosus*, as a rule, disappeared more quickly from the blood and tissues of immunized than normal rabbits.

V. *The Mechanism of Gall-bladder Infections in Laboratory Animals.* As in the other articles in this series this communication by MEYER, NEILSON and FEUSIER (*Jour. Infect. Dis.*, 1921, xxviii, 456) is very comprehensive, embracing detailed observations on the elimination of *Bacillus typhosus* in the hepatic duct bile of normal and immunized rabbits, guinea-pigs and dogs provided with temporary common-duct fistulas and including an extensive review of the literature. The experiments showed that more organisms appeared in the bile of normal rabbits receiving intravenously from 8000 to 24,000 millions typhoid bacilli than in that of immunized animals of the same litter, in the event that the last dose of vaccine was administered twenty to thirty days prior to the infection. The elimination of the bacteria by the hemato-hepatogenous or descending route was immediate. The writers believe that the transit of bacilli from the hepatic bloodvessels to the biliary capillaries is probably governed by the phagocytic action of the endothelial cells. Immuniza-

tion of rabbits prevented to a certain degree the passage of the bacilli, particularly in guinea-pigs but to a less extent in dogs. It is their opinion that the removal of bacteria from the circulation in the first ten to sixty minutes may be the result of an *in vivo* agglutination, the action of blood platelets, or purely a dispersion phenomenon of two colloids and that the leukopenia of the peripheral blood subsequent to the bacillar injections is the result of an uneven distribution of the leukocytes, which are chemotactically attracted by the masses of bacilli collecting in the viscera. Histologic evidence was presented which indicated that the gall-bladders of about one-third of the rabbits inoculated with large numbers of *Bacillus typhosus* received the infection through the terminal capillaries of the mucosa. The transverse route of bile infection through the walls occurred also after ligation of the cystic duct. Direct gall-bladder injections produced an infection of the wall along the lymphatics of the mucosa, submucosa and subserosa. In case the bacteria reach the gall-bladder by the hemato-hepatogenous route only, they multiply in the cystic bile, which is suitable for their development. Rabbit typhoid carriers may be classified into temporary or convalescent and chronic carriers. Thirty to 40 per cent of the intravenously inoculated animals recover in the first month. About 10 to 15 per cent may retain bacilli in gall-bladder for six to twelve months, the persistence of the organisms depending on the degree of inflammation provoked. Chronic carriers probably result from embolic, capillary invasion of the wall, with subsequent transverse infection of the bile. Persistence of bacteria is favored by the formation of biliary calculi, by the extension of the inflammation to the cystic ducts and by a severe cholecystitis, leading to a loss of contractibility of the wall, followed by a state of empyema. Intrasplenic injections regularly produced persistent gall-bladder infection. The insertion of sterile gall-stones into the rabbit gall-bladders led to a secondary infection by "indifferent" streptococci.

VI. *The Reaction and Physiology of the Hepatic Duct and Cystic Bile of Various Laboratory Animals.* By collecting hepatic duct bile from temporary common duct fistulas and cystic bile at necropsy or laparotomy, NEILSON and MEYER (*Jour. Infect. Dis.*, 1921, xxviii, 510) found that the hepatic duct bile of rabbits was alkaline to litmus and frequently to phenolphthalein, the  $\text{Ph}+$  varying between 7.4 to 7.7, while that from guinea-pigs was strongly alkaline to litmus and faintly acid to phenolphthalein. In rabbits, the H-ion concentration decreased on exposure to air, on standing, even to  $\text{Ph}+$  9.2, the decrease probably the result of an escape of  $\text{CO}_2$  and the absorption of ammonia. The reaction of rabbit gall-bladder bile may be acid, neutral or alkaline, but was always acid to phenolphthalein, being influenced by health and diet, ranging from  $\text{Ph}+$  6.4 to 7.7. A high H-ion concentration was produced by fasting and acid forming diets. Hepatic duct and cystic dog, cat, goat and monkey bile differed in reaction, the gall-bladder bile being more variable and tending to the acid side, while the cystic bile of oxen, sheep and pigs was faintly alkaline to litmus. The biles from typhoid, paratyphoid or streptococcic infected gall-bladders of rabbits were alkaline to litmus and half of them also to phenolphthalein. Purulent gall-bladder specimens in some instances showed, on standing, a stationary or increasing H-ion concentration, which, the authors believe,

was due to lactic acid formation, provoked by the disintegration of cellular material. The average daily rate of bile flow in rabbits was about  $\frac{1}{8}$  to  $\frac{1}{10}$  of the body weight (10 cc per hour). Intravenous injections of sodium taurocholate produced a transient cholagogue effect in rabbits, dogs and cats. The authors discuss the mechanical and chemical function of the gall-bladder.

VII. *The Bacteriostatic and Germicidal Properties of Bile.* After an exhaustive resume of the literature and a minute study of specimens of bile of many animals and man, NEILSON and MEYER (*Jour. Infect. Dis.*, 1921, xxviii, 542) found that the hepatic duct bile of rabbits collected in open tubes and seeded with various pathogenic and nonpathogenic intestinal bacteria exhibited selective germicidal properties. The members of the typhoid, dysentery, paratyphoid group remained viable for seventy-two to one hundred and twenty hours, while *V. cholerae* and staphylococci lived for over seven to ten days. A small number of bacteria was more easily destroyed than a large number. True gall-bladder bile, specimens collected from the same animals and tested under the same experimental conditions, failed to exhibit germicidal properties in the chosen time interval of ten days. Typhoid bacilli showed a high degree of viability in human hepatic duct and cystic bile. The authors believe that the bactericidal properties of hepatic bile of rabbits and guinea-pigs is not due to bacteriolysins or a "substance sensibilatrice" and that its H-ion concentration is only indirectly responsible for its antiseptic properties. The initial "lag" in fresh bile is slight and of short duration. Bile collected in open tubes or exposed from four to twenty-four hours to air became germicidal in a shorter time interval than fresh bile, the inoculated microorganisms being destroyed in twenty-four to forty-eight hours or less. Comparisons of the relative bacteriostatic and bactericidal properties of bile from the various animals are made freely by the investigators. They remark that the vigor of the bacterial growth in an average human cystic bile is noteworthy and that proliferation can be influenced by artificially reducing the H-ion concentration. They conclude that their observations have demonstrated, in their opinion, "one standing fact, namely, a test-tube experiment may be simple and reveal a great deal of information, but it does not always tell the truth and may be most misleading."

VIII. *The Influence of the H-ion Concentration on the Growth of Bacillus Typhosus in Media Containing Bile Salts.* SCHOENHOLZ and MEYER (*Jour. Infect. Dis.*, 1921, xxviii, 588), while conducting experiments with bile and bile salts at varying H-ion concentrations to study the rate of growth of *Bacillus typhosus* and its generation time, found that a low H-ion concentration inhibited the growth-stimulating properties of the bile and its salts and rendered such a medium germicidal. Fifty cubic centimeters of medium were seeded with 0.5 cc of a 1 : 10,000 dilution of a young culture of *Bacillus typhosus* in 1 per cent ox-bile salt-free veal broth and incubated at 37° C. At hourly intervals the determination of the number of organisms present was made by plating in peptic digest agar. Bile of oxen, hepatic duct bile of rabbits, bacto "desiccated ox bile," and sodium glycocholate and taurocholate in 1 per cent concentration in a 0.01 per cent "Difco" peptone—phosphate solution at a  $P_h$  7.0 were observed to be growth-enhancing for *Bacillus typhosus*, while greater amounts, such as 3 to 30 per cent, greatly inhibited proliferation.

At  $P_h$  8.4, the same bile specimens or their salts acquired either inhibitive, bacteriostatic or germicidal properties. The more concentrated the biliary salts the greater was their effect on the viable cells. Even small amounts of bile salts, such as 0.5 per cent, destroyed the bacteria in twenty-four hours. At  $P_h$  8.4, glycocholates were more antiseptic than taurocholates, while the same salts in the same concentration could be stimulative at  $P_h$  7.0.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**The Essentials of Smallpox Vaccination.**—LEAKE and FORCE (*Public Health Reports*, 1921, xxxvi, 1975) emphasize the significance of the vaccination reaction, saying: "Absence of this reaction indicates that the virus is incapable of protecting against smallpox, and not that the subject is immune." This reaction may be primary vaccinia or an accelerated reaction in those who retain some degree of immunity from previous vaccination or an attack of smallpox. The accelerated reaction appears earlier than primary vaccinia, is shorter in duration, and decreased in severity by comparison. The necessity for keeping the vaccine on ice is stressed and the technic of the operation by linear incision or by the drill method is given. Dressings are forbidden and a form of certificate is prescribed.

**Direct Inoculation Test for B. Botulinus Toxin.**—BENGSTON (*Public Health Reports*, 1921, xxxvi, 1665) has devised a rapid method for detecting the presence of botulinus toxin in food. The procedure contemplates the inoculation of a series of animals with varying doses of the juice of the food under examination. Certain of the animals are protected by the two types of botulinus antitoxin, the remainder serving as controls. The diagnosis may be made well within a day in certain cases. ORR (*Jour. Infect. Dis.*, 1921, xxix, 287) has found that the intraperitoneal injection in white mice of at least 100 m.l.d. of botulinus toxin produces symptoms of botulism usually in from two to four hours, and death follows the appearance of symptoms within from one to two hours. He used the following method for determination of type: A number of white mice were injected with about 0.5 cc of the filtrate of the infected food, some of the mice having been previously injected with type A and some with type B antitoxin. If the food contains the toxin of *Bacillus botulinus* type A the mice

receiving no antitoxin and those receiving type B antitoxin will die, while those receiving type A antitoxin will survive. On the other hand, if the food contains toxin of the type B organism only those receiving type B antiserum will live. In this way both the presence and the type of toxin may be determined in from four to six hours.

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**I. The Occurrence of Tularemia in Nature as a Disease of Man.**—FRANCIS (*Public Health Reports*, xxxvi, 1731) has adopted the name tularemia for infections with *Bacterium tularense*. The infection is popularly known as deer-fly fever. The clinical histories of a number of natural infections are given. The disease is initiated by the bite of a blood-sucking horse-fly, *Chrysops discalis*, which has previously bitten an infected jack-rabbit. A local lesion, suppurated, often occurs at the site of the bite and in the lymph glands which drain the area. "The fever is of a septic type, lasting from three to six weeks, and convalescence is slow." **II. Experimental Transmission of Tularemia by Flies of the Species *Chrysops Discalis*.**—FRANCIS and MAYNE (*Public Health Reports*, 1921, xxxvi, 1738) succeeded in experimentally conveying tularemia by flies, and give in detail the laboratory data. Flies may remain infected at least fourteen days. **III. Experimental Transmission of Tularemia in Rabbits by the Rabbit Louse, *Hemodipsus Ventricosus*** (Denny).—FRANCIS and LAKE (*Public Health Reports*, 1921, xxxvi, 1747) succeeded in transmitting tularemia by the bite of the rabbit louse in a large percentage of attempts. The lice may remain infected as much as three days. It was shown, incidentally, that the urine and the nasal secretions of rabbits are infective.

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**The Difficulty in Making Differential Diagnosis Between Encephalitis Lethargica and Botulism.**—GEIGER (*Public Health Reports*, 1921, xxxvi, 1663) calls attention to the possibility of confusing the two diseases mentioned on clinical grounds, but insists on their non-identity. A case is reported in which the botulinus organism was isolated from the central nervous system.

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**Reactions of the Nasal Cavity and Postnasal Space to Chilling of the Body Surface. I. Vasomotor Reactions.**—MUDD, GOLDMAN and GRANT (*Jour. Exp. Med.*, 1921, xxxiv, 11) state that chilling of the body surface causes reflex vasoconstriction in the nasal cavity and nasopharynx, as it does also in the oropharynx, palate and tonsils. Re-warming is closely followed by partial, though, except in the tonsils, incomplete recovery of normal blood supply. Irritation of the nasal mucosa by the experimental procedure caused pain and discharge of clear mucus, sometimes also lacrimation and sneezing. The rhinorrhea occurred both on the side directly irritated and on the opposite side, although on the former more abundantly, and was apparently little if at all affected by the diminished blood supply and shrinkage of the mucous membrane incident to chilling the body surface. Discharge from the nose has been at most a rare occurrence in experiments in which the nasal mucosa was not directly irritated. The thresholds of the chilling vasoconstrictor reflex to the mucous membranes of the upper respiratory tract and to the skin of the trunk have been found to be lower than the threshold of the like reflex to the skin of the forehead.



Disrobing the warmly wrapped subject in a room a little below ordinary room temperature has been found sufficient to cause marked vasoconstriction in the sites of the former group, but only slight or no vasoconstriction in the forehead. For relation of these reactions to upper respiratory infection, see *Annals of Otology, Rhinology and Laryngology*, 1921, xxx, 1.

**The Claim that Some Typhoid-Paratyphoid Strains Survive the Milk Pasteurization.**—KRUMWIEDE and NOBLE (*Jour. Infect. Dis.*, September, 1921, xxix, 310) quote the statement of Schorer and Rosenau that the thermal death-points of the pathogenic organisms that may render milk dangerous have been determined with precision in many laboratories and that an actual exposure to 60° C. for twenty minutes would suffice to kill such non-sporebearing organisms as *Bacillus diphtheriæ*, *Bacillus tuberculosis* and *Bacillus typhosus*, voiced the general conclusion of all who had worked on this subject. Although the practical application of these facts to the pasteurization of large volumes of milk was another problem, exposure to this temperature, for the time given, had been uniformly considered as adequate, and this aspect of the subject was looked on as closed. Recently, however, Twiss has reopened the subject and used bacteria of the typhoid-paratyphoid group as test organisms. Her contention is that, in actuality, the temperatures of pasteurization are inadequate; that the method of using small samples of the heated milk for the determination of the death of the bacterium present does not exclude the possibility of the survival of a few organisms. She asserts that if the whole test sample (100 cc) be incubated it will not infrequently be found that a few bacilli have survived exposure to 60° and even to 65° C. for thirty minutes. The practical importance of the question immediately presented itself to the authors, and they began testing a series of cultures from different sources. Twenty-seven typhoid cultures recently isolated from carriers, 7 paratyphoid A cultures, 12 paratyphoid B. cultures and 4 enteritidis cultures were subjected to experiments, using the ordinary temperature of pasteurization. They conclude that there is no evidence that bacilli of the typhoid-paratyphoid group, even in small numbers, will survive heating to 60° C. for twenty minutes. To ensure actual heating of all the sample and to exclude other sources of error in laboratory pasteurization the sample container should be completely submerged in the bath.

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ORIGINAL ARTICLES.

THE NON-OPERATIVE TREATMENT OF CHRONIC EMPYEMA.<sup>1</sup>

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JUST two years ago I read a paper before the College in which I tried briefly to indicate some of the advantages which civil surgeons might derive from four years' experience in military surgery, and tonight I shall endeavor to show that in one field at least the predictions made then have been realized.

Chronic empyema represents one of those conditions which has taxed surgical ingenuity to the utmost, and which has demanded for its cure operations which, in their turn, are accompanied by a high mortality and if successful still leave the patient crippled and handicapped for the more arduous occupations and recreations of life. I refer to the extensive rib resections which bear the names of Estlander and Schede, the decortication of the lung, of Fowler, and any of the other methods employed for carrying the chest-wall into the lung or bringing the lung out to it. Of course other less severe methods, such as the injection of Beck's paste, have caused some of the smaller cavities to heal, but success has been limited and failure has been followed by the more formidable plastic operations.

It is a wise man who profits by his misfortune and the same may be said of a race or generation. Within the past few years the world has passed through its greatest misfortune within the memory of

<sup>1</sup> Read before the College of Physicians of Philadelphia, April 26, 1921.  
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man, the World War. Surgery has always profited by war—in experience, in new devices, in discoveries and in new methods of treatment—and the great world struggle of five years registers no exception, for the treatment of wounds has been revolutionized and the treatment of infections enormously advanced.

Before this war a surgeon who dared to close without drainage a penetrating wound of the chest would have been liable to suit in case of death, and yet today a failure to close such a wound completely would be looked upon as a surgical mistake. The attempt to sterilize a suppurating pleural cavity is no new idea (Beck's paste and Murphy's formalin injections), but it was the war which brought about its practicability and realization.

Chronic empyema, except the tuberculous type, results from an uncured acute infection of the pleura or from the presence of a foreign body in the pleural cavity. The foreign bodies which prevent healing are not confined to the missiles of warfare, as those of you know who have removed drainage tubes which had been "lost." We have all dreaded these old suppurating pleural cavities and our patients have often passed from the hands of one surgeon to another, hoping their next operation would be their last; only too often it is.

The horrible shell-wounds of the thorax gave the military surgeon a wonderful opportunity for study, and the advance that was made in this field of surgery was one of the greatest that has ever been made. At the close of the war fairly definite rules could be laid down for the treatment of these cases. There was a large group which required no operation whatever, those operated upon were closed completely and the cases which later suppurated were subjected to some method of sterilization. These rules need not be rehearsed here, nor need anything be said of Dakin's solution or the Carrel method of employing it. The journals, recent monographs and text-books have made them known to all.

The application of the Carrel-Dakin treatment in acute empyema has also been extensively discussed in the recent surgical literature, and I am of those who believe that every case of acute empyema if it survives the immediate result of infection can be sterilized and cured by the painstaking employment of this method of treatment, and I share the hope of others that it will become more generally used, for I believe that its intelligent use will reduce enormously the cases of chronic empyema.

Since January, 1919, when I returned to the practice of civil surgery, I have operated upon eighteen cases of acute empyema and in all I have started the Carrel-Dakin treatment usually within forty-eight hours after the drainage of the cavity. Except one case that died and two recent cases still in the hospital, sterilization and healing have taken place in all but one, who is tuberculous and still has a little drainage, although he is working and earning his living. I admit that such experiences might be readily duplicated by simple

drainage, especially in children. My youngest patient was eighteen years of age and the others ranged between twenty-one and fifty. I am convinced by my previous experiences that some of these patients who had large collections of pus of weeks' duration would have remained unhealed today under the old method of treatment.

In view of the fact that the chronic case follows the acute one, I think that it may not be amiss to refer to recent changes in the treatment of the acute case which I believe tend to the prevention of the chronic condition. In the first place, I no longer try to make a low opening into the cavity because a low opening makes it difficult later to keep the cavity filled with the solution except with the patient in the recumbent position and sometimes only with the chest lower than the pelvis. I think that the opening in the chest-wall should be made at a point over the collection of pus, which will enable one after the operation to keep the cavity filled with Dakin's solution even when the patient is sitting up or on his feet. In recent cases I have not made a rib resection but simply an intercostal incision, and I have given up attempts to remove from the cavity large masses of lymph and the liberation of the lung by digital separation of the adhesions. If the lung will expand in old chronic cases, where it has been bound down for months and years, when the cavity is sterilized and closed, it has seemed to me that it would do so all the more readily in the acute case, and I am sure that it does do so. These changes, then, render the operation in the acute case much simpler and I believe tend greatly to reduce the mortality.

To Depage, of Brussels, belongs the credit of demonstrating that an empyema of long standing of any size may be rendered sterile with Dakin's solution and then closed or allowed to close. I look back to February, 1918, with the greatest satisfaction, when, at a surgical meeting in Paris, Tuffier exhibited some twenty-five cases of empyema, nearly all of gunshot origin, which he had cured by this method, and I consider it one of the most valuable contributions to chest surgery. He generously gave Depage all the credit. One of his cases seemed quite remarkable and the recollection of it has saved me discouragement and caused me to persevere in a number of very troublesome cases which I have since encountered.

Tuffier's case was that of a soldier whose cavity, after a shell injury and infection, occupied nearly the whole of the right chest and was of many months' duration. It was sterilized and closed, only to fill up and reopen in a month or two, when however a Roentgen-ray plate showed the cavity to be one-half its original size. It was again rendered sterile by the Carrel-Dakin method and again closed, but once more it refilled and reopened. The Roentgen-ray plate on this occasion showed the cavity to be one-fourth its original size. For the third time it was sterilized and closed and had remained closed, the last plate showing complete expansion of the lung. My feeling on seeing and examining this case was that any chronic empyema

could be successfully treated in this manner, and my experience since, in spite of one or two very discouraging cases, has confirmed this belief. Even some of my acute cases have been very obstinate, but I believe that I have learned the usual causes of delay or failure and that they have their origin in faulty technic. The slides which I show demonstrate what can be done in chronic empyema and that success depends entirely on how closely one adheres to the principles of the Carrel technic.

One of the most common objections to this method has been that it is troublesome and requires more attention than the average patient is apt to get in the hospital ward or his home. That such an objection is absolutely groundless is shown by the fact that two of the cured cases—the slides of which I show—carried out their own sterilization at home, obtaining fresh Dakin's solution at the hospital every two or three days. An intelligent and persistent patient can accomplish far more than an indifferent interne or over-worked nurses. It requires enthusiasm and persistence and without these failure is sure to result.

The most important points in the treatment are to bear constantly in mind that, in order to accomplish the sterilization, the Dakin's solution must remain in constant contact with the *entire* wall of the abscess cavity, that the solution must be properly made and fresh, and that the greatest care must be exercised to prevent reinfection of the sinus and cavity from the skin. To the neglect of one of these three things I attribute all of my own failures or delays. The delayed sterilization and closure in the acute cases, also, has been due to neglect in one of these three particulars. The low opening and the bed-rest have been potent factors in preventing the contact between the solution and all parts of the abscess cavity. One patient, an acute case, was many weeks in closing, due entirely to the fact that I had made the opening over the lower part of her cavity and that after operation she was not kept in the recumbent position but was allowed to sit up in bed and used the bed-rest for a greater part of the time. She healed promptly when she was made to occupy constantly a position which enabled us to keep the cavity filled with the solution. Again I have experienced delay in sterilization owing to the use of Dakin's solution which was too old. Reinfection of the cavity from failure to keep the surrounding skin sterile can be easily demonstrated by taking smears from the cavity, the sinus and the surrounding skin.

If cases such as shown by Tuffier, three years ago, and such as I show now can be cured, we should be able to cure practically all cases. A study of our failures will do more to improve our results than a complaisant contemplation of our successes. I have failed in certain cases where the infection was due to the tubercle bacillus, and in others where a persistent sinus had followed the Estlander or Schede operation. I have one case still under treatment after

fifteen months. This man came under my care in November, 1919, about a year after his operation for empyema. He was running a continuous fever and had a cavity that would hold six or eight ounces. It was sterilized and closed in four weeks, but opened up again in another three or four weeks. Since then the sinus has opened and closed several times and it is open now, but the patient has gained weight and has been at work for six or eight months.

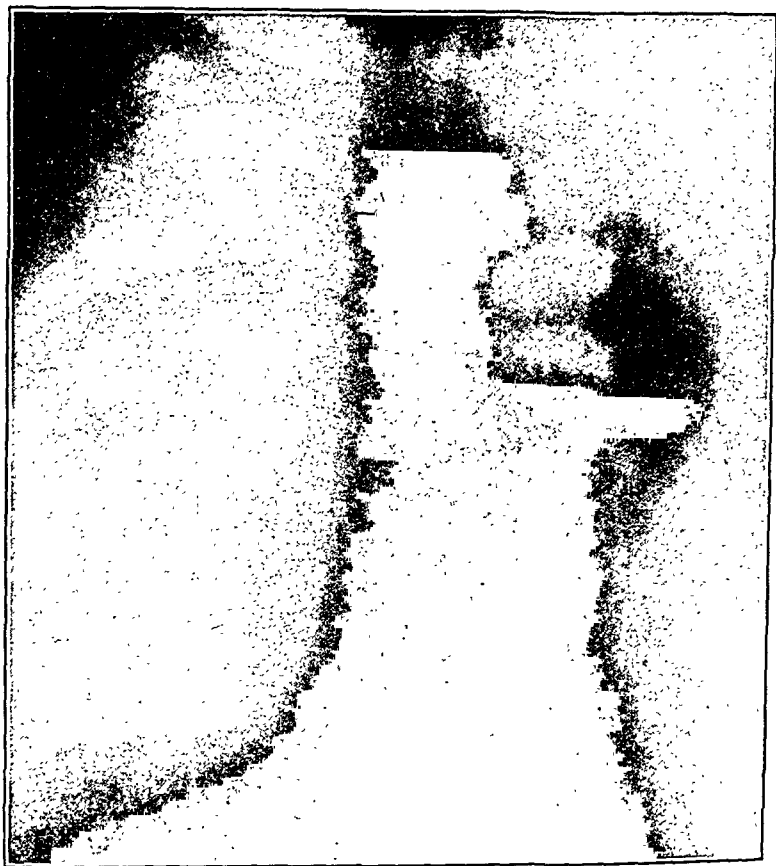
The plan of treatment in the chronic case has been as follows: The capacity of the cavity is estimated by filling it with the patient in such a position that the mouth of the sinus is higher than all parts of the cavity; its exact position and shape have been determined by injecting bismuth in oil and taking stereoscopic Roentgen-ray plates. When this has been done we know the position which the patient should occupy during the treatment in order to keep the Dakin's solution in contact with every part of the cavity. This I consider one of the most important points in the treatment.

The question of operation is now considered. In the absence of necrosis of the rib or the presence of a foreign body no operation has been found necessary in our cases, unless a dilatation of the old sinus may be considered an operation. It is only necessary to make the sinus large enough to accommodate two or three Carrel tubes. Several of our cases have been cured with a single tube in the sinus and I have never had any trouble from contracture of the sinus. In the beginning of the treatment, if more than one tube is used, one of them is left open at the end or a catheter is used in order to permit a thorough washing out of the cavity once a day. The cavity is then kept filled with the solution, just enough being added every two hours during the day and every three hours during the night to keep it full. The tightness of the sinus around the tubes and the correct position of the patient should prevent the escape of the fluid. Unless care is given to the regular instillation of the fluid there is no use in trying this treatment, as failure will certainly be the result.

With the apparent disappearance of pus, smears are taken from the depth of the cavity and from the sinus. When these smears are negative for three or four consecutive days the tube is withdrawn regardless of the size of the cavity, and the sinus and the skin about it kept sterile with iodine until closure takes place. I do not think it is necessary to close the wound and I am almost sure that it is better not to do so. The operation may cause the liberation of dormant organisms in the tissues about the mouth of the sinus which in turn may cause a reinfection. Such infections were constantly seen in plastic operations done months after the complete healing of gunshot wounds. If the cavity and sinus are not sterile when the tube is removed, pus will soon be found again in the discharge and the tube can readily be reintroduced. If a closure has been made and the cavity is not sterile one only discovers it by

physical signs and fever, and before these develop the old cavity has become distended with pus. If a reaccumulation of pus occurs after closure or after healing of the sinus, as certainly will occur in some cases, the tubes must be reinserted and the sterilization repeated. I have had this experience several times in the acute cases.

It has been suggested that Dakin's solution causes bleeding and I have seen it in a few chronic cases. I do not think that it is apt to occur until the cavity is sterile, and if no organisms are present in



CASE I.—March 7, 1919. (See page 476.)

the smears from the cavity and sinus the tube should be withdrawn and the sinus treated with iodine until closed. If bleeding occurs and organisms are still present, normal salt solution should be used for a time and then the Dakin's solution resumed.

Bronchial fistula is a very troublesome complication and renders the treatment difficult. I have had but two such cases and in both the opening into the bronchus closed with simple drainage of the cavity or under salt solution irrigation. The first chronic case we

treated (Case I) had a bronchial fistula and it healed while the Dakin's solution was being used. I think that unless the fistula is large and the cavity a very old one it will usually heal if the cavity is kept empty. It may be necessary in these to make a low opening in order to get drainage, but I have not had to do it. We often see these fistulæ heal after the drainage of a lung abscess.

The following five cases (I have not included cases operated upon or treated by my assistants) illustrate the points I have tried to



CASE I.—April 26, 1920. Wound closed since September, 1919. (See page 476.)

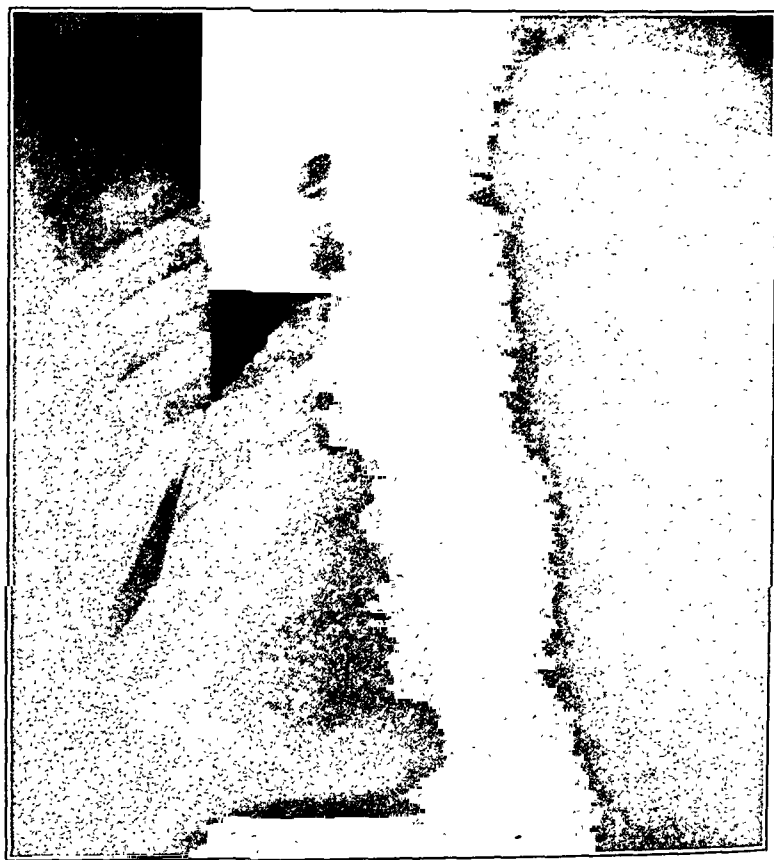
make and constitute my experience in the chronic condition—with the exception of three other cases, in one of which there is a tuberculosis of the lung, in another a large cavity was lined with a thick shell of bone, and in the third an extensive plastic operation had been done and a long narrow sinus remained. The tuberculous case is still under treatment with a regularly diminishing cavity, the calcareous case died two months after an extensive plastic operation, and the third case has disappeared.

This experience is not large, but owing to the better treatment



of acute empyema one does not see so many of the chronic cases. I feel, however, that it is large enough to show that we have in this treatment—which originated in the war—the best method of dealing with the chronic empyema of civil life, and that it should be conscientiously tried before resort is had to the formidable and mutilating plastic operations.

Before undertaking the treatment I think that one should familiarize himself with the details of the Carrel technic. In the beginning



CASE II.—April 15, 1919. Patient on right side. (See page 478.)

failure is sure to be met; the one failure and the repeated delays in my own experience have been due I am sure to my own faults in technic already referred to.

CASE I.—C. B. W., aged thirty-eight years. Pennsylvania Hospital. This patient came under my care March 29, 1919. In May, 1918, he had a pneumonia followed by an empyema, which “pointed” in the interspace just below the left nipple and was

simply incised by his physician. Since this time he has had more or less continuous drainage and fever. As soon as the sinus closed the patient expectorated pus, but this stopped when the sinus opened again. The pus from the cavity shows streptococci, staphylococci and pneumococci. The sinus was injected with bismuth and oil and excellent stereoscopic plates were made by Dr. Manges. The outline of the cavity is irregular and extended posteriorly up under



CASE II.—April 15, 1919. Patient on back. (See page 478.)

the scapula and as far down as the tenth rib. The communication with the bronchus is also shown in the plates. After this examination the patient coughed up at once a considerable amount of bismuth and oil. The empyema was evidently of the interlobar type. Under gas anesthesia a portion of the sixth rib and its cartilage, both of which were diseased, was removed and the sinus dilated until it admitted a finger easily. Considerable bismuth and oil were evacuated and two tubes were introduced. The Carrel-

Dakin treatment was begun three or four days after the operation and the patient was discharged from the hospital on May 5th. At this time there were still organisms in the smears but the patient was much improved. From this time until his complete cure the treatment was carried out at his home by his wife, the Dakin's solution being obtained fresh from the hospital every two or three days and the patient reporting once a week. The sinus closed in August but reopened in September; it closed again after a week or two weeks and has remained closed ever since. The patient gained

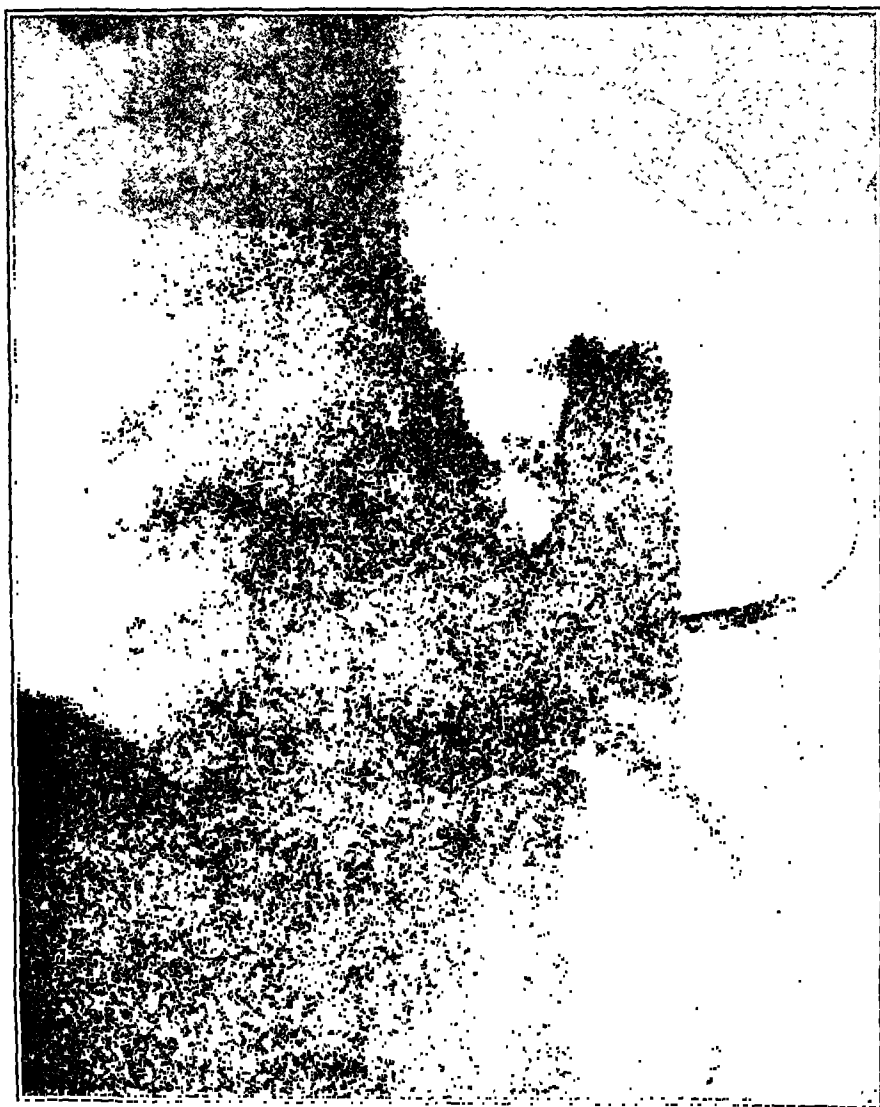


CASE II.—April 20, 1920. Wound closed since September, 1919.

about forty pounds in weight during the course of his treatment and carried on his work, that of manager of a large farm. Recent examination shows perfect function with complete expansion of the lung and these findings are confirmed by a Roentgen-ray plate.

CASE II.—W. R. L., aged thirty-five years. Pennsylvania Hospital. This patient came under my care April 7, 1919. He had an empyema which had been drained with rib resection in September, 1918, in another hospital. The empyema had developed insidi-

ously the previous May. Drainage has kept up ever since operation and the patient has fever off and on. Injection of the cavity and Roentgen-ray plates showed it to be very large and to extend posteriorly as high as the second rib. It was evidently of the interlobar type. He was admitted to the hospital, April 14, 1919, the sinus was dilated without an anesthetic, bismuth, oil and pus evacuated, and the

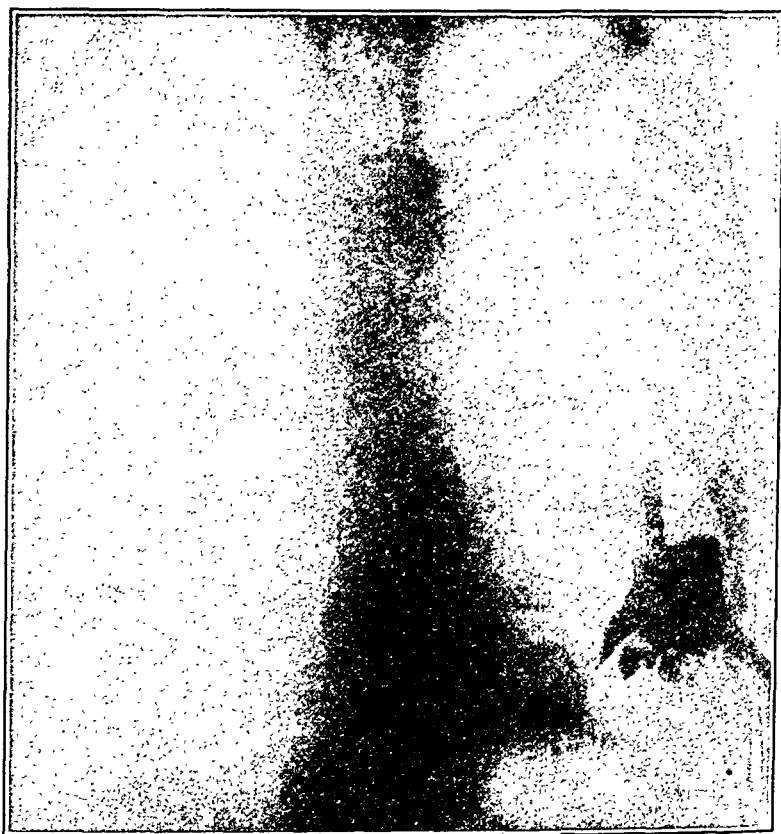


CASE III.—November 3, 1919. (See page 480.)

Carrel-Dakin treatment started. After about three weeks he went home, where a sister, who was a trained nurse, carried out the treatment. The sinus in this case was four and one-half inches long and the length of the cavity three inches. A catheter was employed for the instillation of the fluid. The sinus closed in September and has remained closed since and there is good expansion of

the lung. Patient gained about ten pounds in weight and went back to work in July. In this case the opening of the sinus was far below the cavity, but the patient was made to keep the recumbent position after each instillation of the fluid and the tightness of the sinus about the catheter tended to prevent the escape of the solution. His chest appears normal on physical and Roentgen-ray examination.

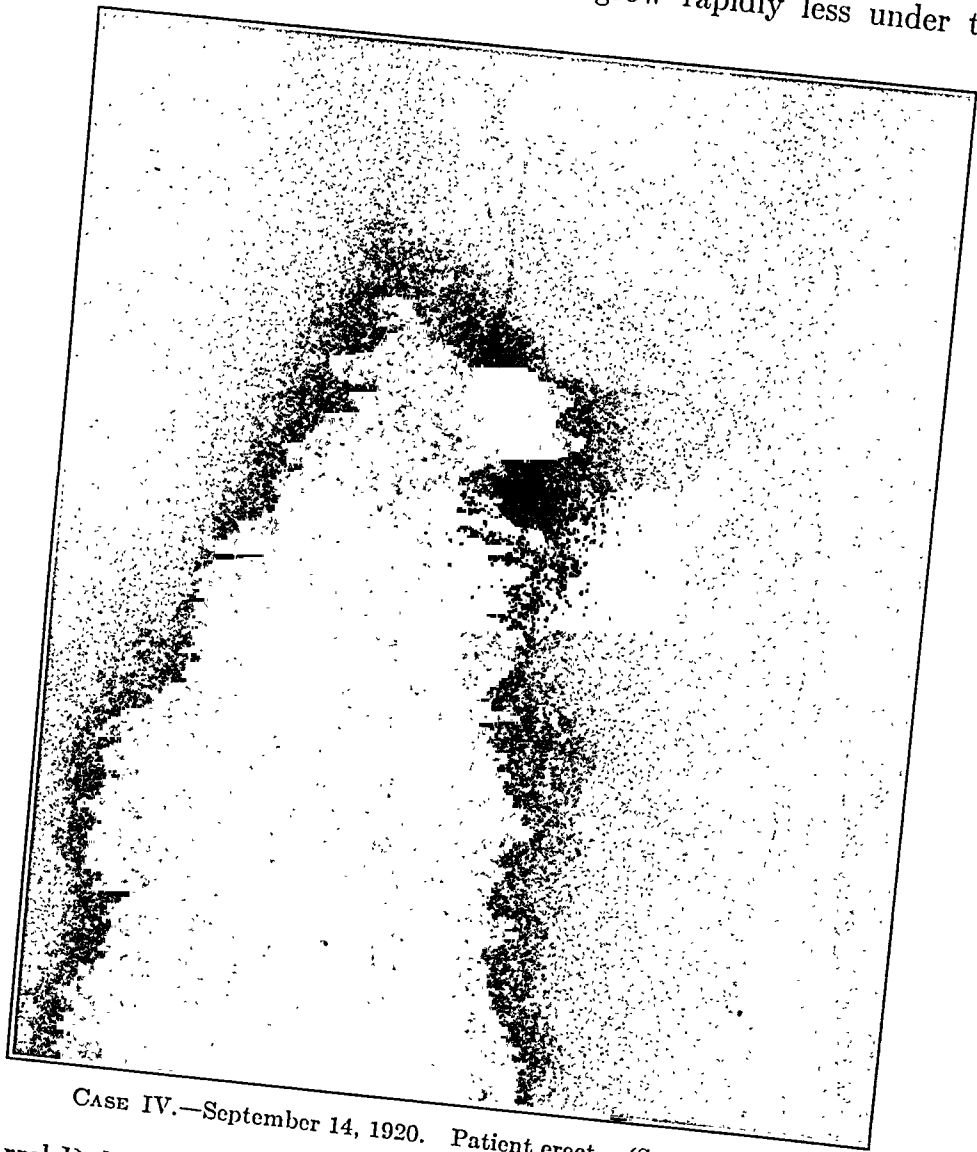
CASE III.—W. W., aged forty-four years. Pennsylvania Hospital. This man was operated upon for empyema on December 4,



CASE III.—March 25, 1921.

1918, by Dr. Stewart. An intercostal incision was made and a double tube inserted. Dakin's solution was employed for a short time. He was discharged March 16, 1919, still draining. He was readmitted on May 16th, when another incision was made to give better drainage. He was discharged on the 25th much improved. He was admitted to my service November 12th, about a year after his first operation. He had fever and a discharging sinus. The plates showed quite a large cavity containing six or eight ounces of

fluid. Carrel-Dakin treatment was commenced, and as smears were negative on three occasions the sinus was closed on December 24th, about six weeks after the commencement of the treatment. It remained closed for about a month when he was readmitted with fever and the physical signs of fluid. His condition immediately improved and the cavity began to grow rapidly less under the



CASE IV.—September 14, 1920. Patient erect. (See page 482.)

Carrel-Dakin treatment. Since this time closure has taken place twice, but each time has been followed by a reaccumulation of pus. For the last six or eight months the man has been at work. This case represents a failure thus far, but I believe if the patient were kept on his back the cavity could be readily sterilized. The patient is loath to give up his work and his general health has improved so much that I have not insisted upon the necessary rest.

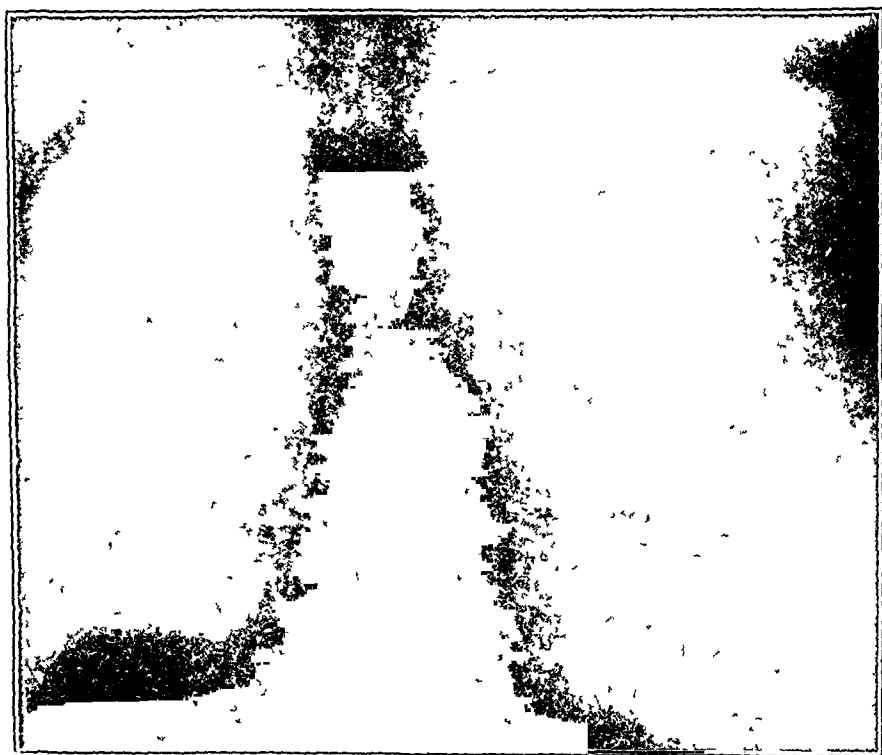
CASE IV.—P. P., aged thirty-four years. Pennsylvania Hospital. This man was operated upon in another hospital March 6, 1920, for an empyema following pneumonia. A rib section and drainage was done. The sinus has remained open ever since. He came into my service on September 13, 1920, six months after his operation. Roentgen-ray plates showed a large cavity. Carrel-Dakin treatment was started and fairly prompt sterilization was



CASE IV.—September 14, 1920. Patient on side.

accomplished, the patient being discharged with the sinus closed on October 25. It has never reopened and the patient has been perfectly well and now has full expansion of the lung, but his Roentgen-ray plate shows considerable bismuth in the lower part of the cavity. I regret that we did not get rid of all the bismuth in this case. However, he demonstrates a quick and complete cure in a chronic condition.

CASE V.—E. S., aged eighteen years. Jefferson Hospital. This boy was operated upon for empyema in a neighboring town in 1912. Several ribs were resected. He was in the hospital seven months and was discharged cured, the wound being entirely healed. He had no trouble for seven years (August, 1920), when a small fragment of bone was discharged. At this time he was admitted to the Pennsylvania Hospital and operated upon by Dr. Mitchell for a necrosis of the third, fourth, fifth and sixth ribs. The sinus was curetted and injected with Lassar's paste. Later a counter-opening was made lower down. He was discharged from the hospital on October 9, the sinus being entirely healed. In January,



CASE IV.—January 7, 1921. Wound closed since October, 1920. (See page 482.)

1921, the upper sinus reopened. He was admitted at this time to the Jefferson Hospital, where a Roentgen-ray examination showed a body of bismuth about the middle of the chest and a smaller portion quite low down near the diaphragm. This bismuth had evidently remained in the chest since last August. When the sinus was injected with bismuth and oil, it was found to communicate with the old bismuth shadow below and there was apparently no communication with that above. The lower cavity was quite large, holding several ounces and communicated with the opening in the chest-wall by a very narrow sinus. There was a fusion of several ribs at the site of the former operations. On February 1, I increased the



size of the opening, removing some bone with forceps, dilated the tract and evacuated considerable bismuth and oil. Long curved forceps passed down through the sinus could be felt quite readily between the ribs six inches below. A Carrel tube and catheter were inserted into the cavity and the Carrel-Dakin treatment started the second day after operation. There was considerable discharge of pus for the first ten days, but has nearly altogether disappeared. The patient is still in the hospital. (Patient developed scarlet fever



CASE V.—January 19, 1921. Wound closed April, 29, 1921.

during his convalescence and treatment was interrupted. Later it was recommenced and on discharge April 29, 1921, wound was closed.)

To summarize these cases, the first two represent cures after a number of months of home treatment, in one of which there was a bronchial fistula; the third case represents a failure so far, although closure has taken place twice; the fourth case represents a prompt sterilization with permanent closure, and the fifth case a cure.

## GASTRO-INTESTINAL INFECTION IN RELATION TO INFECTION OF THE LIVER AND BILE PASSAGES

(A Continuation).

BY CHARLES G. STOCKTON, M.D.,

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**Résumé of Former Report.** In 1916 the patient first appeared, suffering from debility, hypochlorhydria and lowered nutrition; there were no symptoms related to the liver or to the intestine. She was discharged eight weeks later, showing general improvement, and was in good health until the spring of 1919, when there developed intractable diarrhea. She returned to Buffalo in September, 1919, with gastro-enterocolitis of the greatest intensity in the small intestine and with gas bacilli and streptococci abundant. The stomach showed atonic dilatation, achylia, pus cells, red blood cells and an excess of mucus. In November, 1919, the diarrhea was controlled, gastric secretion reappeared and the patient was discharged, taking a smooth diet. Improvement continued for a month, with a gain in weight of fourteen pounds, but she ate too freely and became for the first time jaundiced. On December 24, three weeks later, she came again to Buffalo. There was complete associated jaundice, with acholic stools. A study of the stomach and duodenal contents indicated severe duodenitis. There was a recurrence of diarrhea. The liver was enlarged and slightly tender to pressure, but there was no pain.

**Conclusion.** Biliary obstruction from swelling at the ampulla of Vater.

There was slight elevation of temperature and a leukocyte count of 6100. Duodenal lavage was practised with benefit. The jaundice diminished, became intermittent with occasional rigors, followed by fever and renewed jaundice with leukocytosis. The clinical picture corresponded with the old conceptions of angiocholitis. The intestine, including the colon, showed atony and catarrhal inflammation. Under deep duodenal feeding, duodenal lavage and colonic irrigations the patient improved. In May, 1920, recovery seemed possible, as stated at our last meeting.\*

**History of the Case as Developed Subsequent to the Report Made at the Last Meeting of the Association.** The patient had almost invariably a good appetite. At times there was slight gastric secretion (hypochlorhydria), at other times secretion was absent, with evidence of a low-grade gastritis. Intermittently the stools showed bile coloring matter and bile salts, but not always associated. She was not studied as to the presence of hemoconias.

\* Transactions, twenty-third Annual Session of the American Gastro-Enterological Association, May 3 and 4, 1920. See "Annals of Medicine," vol. 1, No. 2.

In the duodenal contents pancreatic ferments were very deficient. There was feeble amyolytic enzyme, still feebler proteolytic enzyme and usually absence of lipase action. Always there was mucus in excess, occurring often in shreds, containing numerous pus cells, at times many degenerated red blood cells.

It was evident that there was an open passage through the bile ducts, but nevertheless infection coming through the biliary channels. This was proved by the use of the duodenal tube after irrigation of the stomach and duodenum. It was also evident that there was a very defective digestive power in the duodenum as result of the disordered pancreas and the duodenitis. At this time the suggestion was made by Dr. Rose Donk, who was assisting on the case, that the transfusion of normal duodenal contents from a healthy donor might provide the patient with needed digestive ferments and help her to gain in nutrition. This treatment was carried out by Dr. Donk under my observation during a period of two weeks. The healthy donor while fasting, having had passed the duodenal tube and having had the secretions stimulated by small quantities of hot water, gave out from 60 to 200 cc of duodenal contents, which were immediately introduced through a tube into the duodenum of the patient. The result of this treatment was published by Dr. Donk,<sup>2</sup> under the title "Transfusion of Duodenal Contents." The work was interesting, and unquestionably the patient received temporary benefit from the measure. I am convinced that this suggestion made by Dr. Donk will prove to be of some practical importance in selected cases.

Intestinal perfusion was also practised at other times, with apparent benefit. A freer flow of bile was promoted by irrigation with magnesium sulphate solution as suggested by Meltzer. The diarrhea never recurred with its former intensity, yet there was a continued predisposition to looseness requiring attention and at times special medication. The sigmoidoscope revealed a catarrhal colitis but no bleeding-points. The patient in February had a definite intestinal hemorrhage unexplained in origin.

Medical and surgical consultants leaned to the opinion that there was more trouble in the gall-bladder than had been hitherto believed. It was suggested that we were dealing with a chronic cholecystitis with calculi. There was no evidence of this, however, in the radiograms which were shown and discussed at our last meeting. To my mind it seemed clear that the trouble was not from the gall-bladder, but that we had, following the blocking at the papilla in the beginning of the jaundice, an ascending infection which reached the liver and probably the pancreas.

During May the case was at a standstill, with an occasional discouraging relapse; that is, chills, fever and leukocytosis, the

<sup>2</sup> Jour. Am. Med. Assn., November 13, 1920.

attack lasting two or three days; then the jaundice would fade, but it never disappeared. It was decided, finally, that there should be made a cholecystostomy, with the hope that by removing a cholecystitis the infection passing into the intestine would be eliminated and that the patient might be benefited. Also, it would settle the question as to calculi.

The operation was made under gas and ether anesthesia, which was preceded by a transfusion of 750 cc of blood from a well-typed donor. The transfusion was intended not only to strengthen the patient but to increase the coagulability of the blood, which had been found to be fourteen minutes plus. Following the transfusion, Dr. James A. MacLeod operated upon the patient, removing the appendix, which showed chronic inflammation, and performing cholecystostomy. It was decided to do little exploring, so that the shock might be at the minimum. However, it was found that there was no evidence of tumor about the stomach or duodenum; the pancreas was unusually firm on palpation; the gall-bladder was not distended but was rather pale, and contained no calculi, but a small amount of rather dark bile of increased consistency. The liver was apparently moderately enlarged, pale yellow in color, rather firm upon palpation, with the surface irregular as seen in cirrhosis. The common duct was not explored.

The patient endured the operation remarkably well and seemed to be in better condition after it than before, doubtless from the transfusion. The amount of bile drainage was small and we felt that little was directly gained by the operation. For some days, however, the patient did well, when there ensued another, and this time severe, intestinal hemorrhage, and transfusion seemed necessary to save life; 500 cc of blood were therefore introduced into a vein. The blood was taken from a new donor. There was no agglutination shown on typing, but subsequently it was found that the patient's serum hemolyzed the donor's corpuscles. There followed great prostration, with unconsciousness. In the state of depression, amounting almost to shock, which followed the second transfusion with blood, there appeared in the urine a large amount of urobilin. Previously it never had appeared in the urine, and after that event it never disappeared. It is an interesting question as to what effect this transfusion may have had upon the liver to hasten its degeneration in its already crippled and infected state. There is, of course, the possibility of coincidence, but the clinical fact remains striking. For a few days it looked as though the patient would succumb from hemolysis and protein-poisoning. However, she rallied and matters progressed favorably for a few days, although there continued to be marked urobilinuria. At this time drainage of bile was insignificant, and it occurred to me that benefit might follow irrigation of the gall-bladder through the drainage tube, with a magnesium sulphate solution of 25 per

cent. This was practised, with the result that the drainage of dark-colored bile was much increased. There was considerable diminution of the jaundice, which had deepened since the operation. I think that real but transient improvement followed this irrigation of the gall-bladder with a magnesium sulphate solution. This was carried out for a month, the patient making slow improvement. The evidences of infection were less conspicuous—that is to say, there was absence of chills, but a slight temperature. Under the treatment the liver shrank in size and it was difficult to keep a drainage tube in place for purposes of irrigation. Finally, irrigation became impossible, the wound healed and the patient was sent to her home.

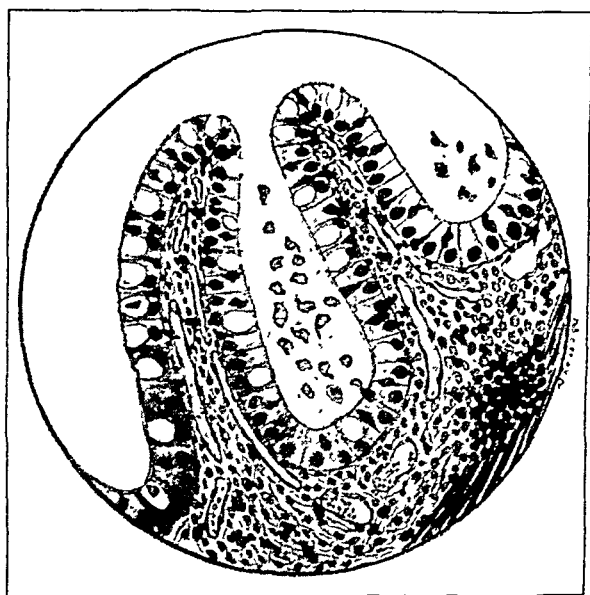


FIG. 1.—High-power sketch of intestine with two villi. Numerous goblet cells among the surface epithelial cells, leukocytes free between the villi and migrating through the epithelium; dilated capillaries, cell collection in the submucosa, all indicating subacute enteritis.

She made the journey of one hundred and fifty miles with little difficulty, and continued with but little change in her condition for about a month, when she somewhat suddenly went into a collapse and died.

Dr. William F. Jacobs, pathologist, accompanied me to her home and there was made a careful but incomplete autopsy, limited to the examination of the abdominal viscera. The results of this postmortem study were interesting. The stomach showed dilatation with gastritis. From the gross appearance the mucous tissues of the duodenum were infiltrated, swollen, intensely red and some-

what softened. This catarrhal state of the intestine was observed throughout the gut, being less evident in the colon than in the small intestine, and more marked in the duodenum than elsewhere. There were no adhesions from the appendectomy. There were the usual adhesions at the site of the duodenostomy. From microscopic sections the tunics of the stomach and intestine showed less inflammatory change than would have been anticipated from their appearance, yet on microscopic section marked duodenitis was demonstrated. The gall-bladder was contracted but showed no growth on culture. The biliary passages, including the common duct, cystic duct and hepatic duct, were healthy. There was no evidence of calculus past or present, nor was there evidence of past cholangitis.

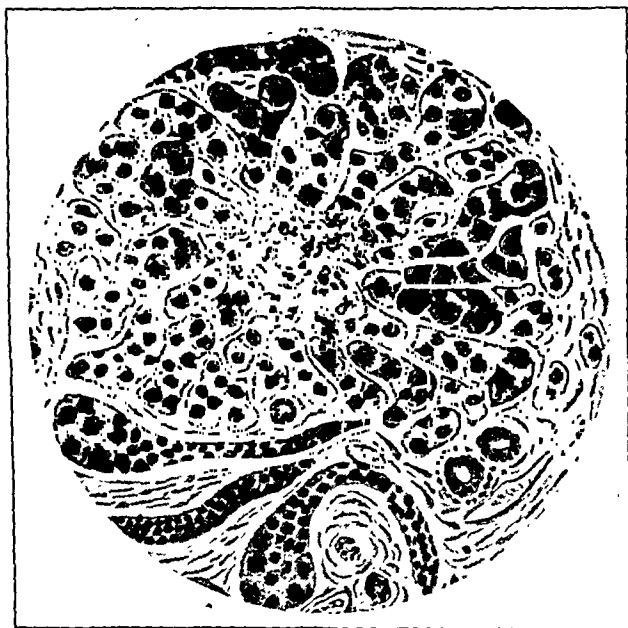


FIG. 2.—High-power diagrammatic sketch of part of a liver lobule, with small central area of necrosis and new-forming bile ducts at the edge.

The striking and interesting features of the case were found in the structures of the liver itself. This organ had shrunk to perhaps two-thirds its normal volume, which it will be recalled was large during the six months preceding the operation, and also at that time. It was yellowish, fawn-colored, with small irregularities of surface, such as one sees in hepatic cirrhosis. On incision of the liver in all parts of the organ there were found countless areas of necrosis, rather dry in character, containing débris. The tissues presented the picture of minute areas of hepatitis, in which the biliary passages escaped except at their origin, as occurs in biliary cirrhosis. There was marked ingrowth of connective tissue

containing many new-formed bile ducts. The pancreas showed but slight interstitial change; there was no evidence of actual infection.

From a strictly postmortem point of view it might seem that the process had begun in the liver and that the bile had led to infection of the intestinal tract. Such a conclusion does not correspond with the history of the case. It will be recalled that the patient suffered primarily from gastritis and failing gastric function, and three years later from enteritis, and was subsequently never free from these conditions. There was no jaundice preceding the last eight months of life. It is my own judgment (and I think the morbid

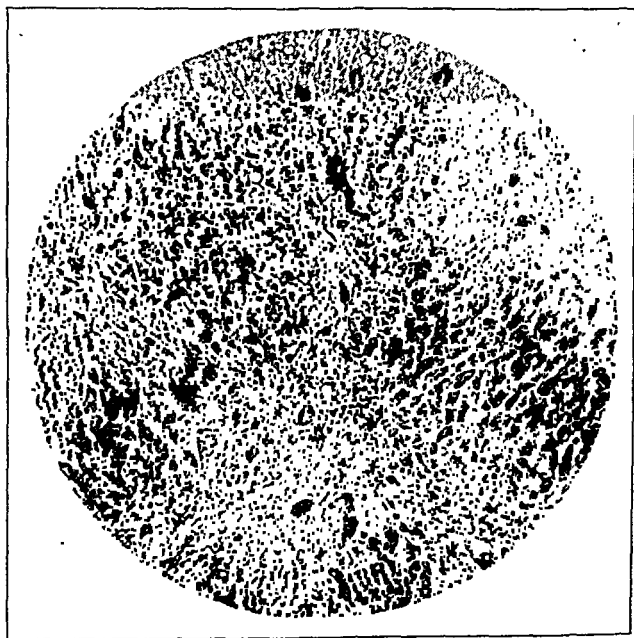


FIG. 3.—Quite low-power photomicrograph of the liver. An area of well-stained liver tissue shading into unstained and necrotic tissue. Also cellular fibrous tissue with bile ducts.

structures support this view) that the disease was primarily a gastritis, later an intense duodenitis; that there was from swelling of the duodenal mucosa, a blocking at the papilla, which caused the first attack of jaundice. Meantime infection had been carried to the liver through the portal system, and thus there was set up a hepatitis with descending inflammation, and not one that ascended through the biliary tract, as I had naturally inferred. I feel that this statement is worthy of repetition and emphasis, for the reason that this case seems to illustrate the growing belief that jaundice is more often the result of an infective or toxic hepatitis, with the infection descending, than an ascending infection; that is to say,

the infection reaches the liver through the portal system, and the obstruction to the outflowing bile occurs in and about the lobules and possibly at the beginning biliary passages. This is not to deny the well-known fact that jaundice often arises from obstruction at the common duct or the hepatic duct, and this obstruction may, of course, be inflammatory. Except in the instance of calculi causing actual obstruction at the junction of the cystic and common ducts or in the ampulla, jaundice is probably rather rare from simple angiocholitis of ascending nature.

There are the following outstanding features to the history of the case:

1. The relationship that may exist between hepatitis with necrotic areas, later replaced by interstitial ingrowth on the one hand, and on the other hand persistent gastro-enterocolitis, in some regions intense.

2. With this pathology, nevertheless, there was escape from involvement or inflammation of the chief bile channels and the gall-bladder, as shown during life by operation and later by post-mortem.

3. The illustration of possibly beneficial results from a novel method of treatment, that of transfusion of the normal duodenal content of a healthy donor into the functionless duodenum of a patient, also the value of intestinal perfusion.

4. The remarkable effect in stimulating the flow of bile from a badly diseased liver by direct irrigation of the gall-bladder with a magnesium sulphate solution. This also is, so far as I know, a novel measure of treatment, and is interesting to compare with the method of stimulating the outflow of bile as described by Vincent Lyon.

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## CALCIFICATION OF THE PITUITARY WITH HYPOPITUITARISM AND WITH SYMPTOMATIC TREATMENT.\*

BY GEORGE E. PFAHLER, M.D.,

AND

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It has been said by someone that the pituitary is the "gland of personality." To this might be added "It is the gland of romance." Not only has it a great deal to do with physical and mental vigor, the stature, form, color and amount of hair, sex characteristics and physical strength, all being controlled by this bean-sized organ

\* Read before the Section on General Medicine, College of Physicians, Philadelphia, May 30, 1921.



tucked away beneath the brain in its own bony casket, but it has to do with romantic things. Without it Leander would not have desired to nor could he have swum the Hellespont to meet Hero. Samson must have had a robust one, so must Goliath, and Delilah's was by no means idle. Physical beauty is entirely dependent upon it, and if this organ is diseased it can make its owner not only hideously ugly, very unhappy, but immoral and even criminal. Several cases of seriously disordered function of this gland with marked calcification of its tissues mostly with hypopituitary symptoms have come to our attention. This is by no means an unknown or undescribed lesion of this organ. In roentgen-ray studies of the skull contents calcareous infiltration has been observed by numerous roentgenologists, in various tissues and structures, notably in tumors, gummata, cysts, aneurysms, walls of arteries, veins of the velum interpositum, old blood clots, cysticerci, the falx cerebri, the pineal and the pituitary. Detailed studies of the latter have been made by Heuer and Dandy,<sup>1</sup> Murphy,<sup>2</sup> Timme,<sup>3</sup> Pick, Boas and Scholtz,<sup>4</sup> Pollock<sup>5</sup> and by Falta.<sup>6</sup> Some endocrinologists believe that calcification of the pineal gland in youth is its terminal stage. To us it seems that this calcification in the pituitary signifies the same pathological condition. In general works on pathology but meager mention is made of this process, save by Delafield and Prudden, and by James Ewing in *Neoplastic Disease*.

Walter Timme, in a personal communication, related that he saw a pituitary gland at postmortem that exhibited a large granule of calcareous matter in its substance. This gland had been taken from a subject that had suffered for years from hypopituitarism of the Frölich type. He has seen other pituitaries with the same infiltration. Boas and Scholtz, in speaking of calcification of the pineal, describe deposition of brain sand in other (endocrine) glands. They say that deposition of calcium in the pineal is serious. Falta describes marked calcareous infiltration in the sella turcica of a eunuch aged twenty years.

McCarthy and Dercum<sup>7</sup> reported a case of hypopituitarism in which at autopsy the gland was found to be completely invested with calcareous matter. In one of the illustrations of Heuer and Dandy's most excellent article the shadow of the pituitary is very dense, evidently calcified, and the clinoidal processes are much obscured or obliterated. Dr. Charles H. Frazier, in a personal communica-

<sup>1</sup> Roentgenography in the Localization of Brain Tumors, Based upon a Series of One Hundred Cases, Johns Hopkins Hosp. Bull., November, 1916, No. 309, vol. 27.

<sup>2</sup> Intracranial Calcification, Am. Jour. Roentgenol., February, 1921, p. 77.

<sup>3</sup> A New Pluriglandular Compensatory Syndrome, Endocrinology, July-September, 1918.

<sup>4</sup> Arch. Int. Med., 1918.

<sup>5</sup> Am. Jour. Oph., August, 1918.

<sup>6</sup> Ductless Gland Diseases, P. Blakiston's Son & Co., 1916.

<sup>7</sup> AM. JOUR. MED. SC., 1902.

tion, related that he operated in 1921 upon a blind youth in whom he found a cyst the arc of which was some 40 mm. above the floor of the sella (the growth was hypophyseal). Its walls in a radiograph made by Dr. Henry K. Pancoast were seen to be densely calcified. This case will soon be published. William Duffy<sup>8</sup> reported the pathological findings of two hypophyseal tumors that contained calcareous granules and crystals, some of which were found previously by Dandy at operation. Erdheim, quoted by Duffy, reported upon two calcified tumors of the hypophysis in which granules of calcareous matter were seen just above the sella in the radiograph. In an adamantinoma of the hypophysis at autopsy, Beck in 1883 found well-calcified teeth. If a radiograph could then have been made these teeth would have been shown. Duffy found uncalcified bone in one of the tumors above alluded to. Heuer and Dandy report in their paper: "Seven certified hypophyseal and two suprasellar tumors, in the roentgenogram of which are definite calcareous shadows. Since tissue removal at operation has in four instances shown calcification histologically we are inclined to consider all the shadows in all the cases to be due to calcification." We too have presumed that all the shadows in our roentgenograms of cases are calcareous. We have no histological evidence to offer. None of our cases came to either autopsy or to operation. Heuer and Dandy's experience seems sufficient data for our tenets, not to mention the other evidence of Duffy, Timme, etc., that we have produced. All that we have in the way of histories in seven of our cases consists of some notes and the radiographs, the subjects being too crippled to come from a distance for further study.

Timme describes an entirely new pluriglandular syndrome (Timme's Syndrome) in which the major element is pituitary disease, mainly under-secretion. In several of the excellent plates which illustrate his article moderately dense shadows are to be seen in the pituitary fossæ, with smallness of the fossæ and a bridging over of the cavities by the clinoidal processes. In some of our cases this same appearance is shown. This latter, according to Timme, crowds in the pituitary and has a great deal to do with the symptomatology of the syndrome. This can be plainly seen in the illustrations which accompany Timme's article, and in Fig. 1 of our cases the confinement of the gland may lead to ultimate calcification. The role of infection of the sphenoid lying below and adjacent to the sella is probably important. In Case I, reported below in detail, early sinusitis was probably the cause of an inflammation of the pituitary with ultimate calcification of it and its enveloping capsule. In most of the cases of calcification a condition of hypopituitarism accompanies the infiltration, but not always. Hyperplasias with hyper-

<sup>8</sup> Ann. Surg., November, 1920.

pituitarism (Timme's stage of compensation) exhibit this degenerative change. Indeed, every variety of dyspituitarism may show this form of infiltration. It may mean but a single manifestation of a pluriglandular sclerosis due to some infection. What pathological process precedes it we are at a loss to say. At any rate it can mean nothing but a final step in a degenerative change.

CASE I (Fig. 1).—This corresponds in many ways to a mild partly compensated form of Timme's syndrome, to which the reader is referred. Mr. X, aged fifty-four years, had long before coming under our observation been considered by his various physicians to be a confirmed



FIG. 1.—Case I, aged fifty-four years. Normal sella. Note the smooth outline of the bony walls, the solidity of the clinoid processes, the clear sphenoidal sinus below and the uniform density both within the sella and outside. Incidentally the arrow points toward a calcification of the pineal gland.

neurasthenic. He had been born of healthy parents, in excellent circumstances and tenderly reared in affluence and culture. His family history in some respects was far from robust nervously. A brother died in youth of dementia precox. An uncle died insane. His parents were too solicitous as to his health and kept him too much indoors lest he should catch cold, which he nevertheless often did in his childhood and youth. He entered college at eighteen years and was promptly dubbed "Sleepy" by his classmates because of his somnolent tendencies (a certain sign of insufficient pituitary function.) Headaches began then and afflicted him for many years; these were mostly occipital. He never had syphilis, typhoid or tuberculosis. He was educated as a clergyman and led an exemplary

life. He is the father of six children, five of whom are living, four being ruddy, healthy youths. One shows signs of early fatigue and some depression at eighteen years, due to too rapid growth. After completing his college course he suffered a nervous breakdown, for which he went to Europe and finally recovered. Again in the late forties he suffered another breakdown lasting two years, from which he again recovered. Symptoms of vagotonia afflicted him in these breakdowns. This expressed itself as a gastric neurosis which at times was so severe as to suggest to his attendants that he had an ulcer of the stomach. Vagotonia, according to Timme, is common in these cases. For thirty years he was miserable because of headaches, early fatigue and depression. He never engaged in any active pursuit, save for a time he was a gentleman

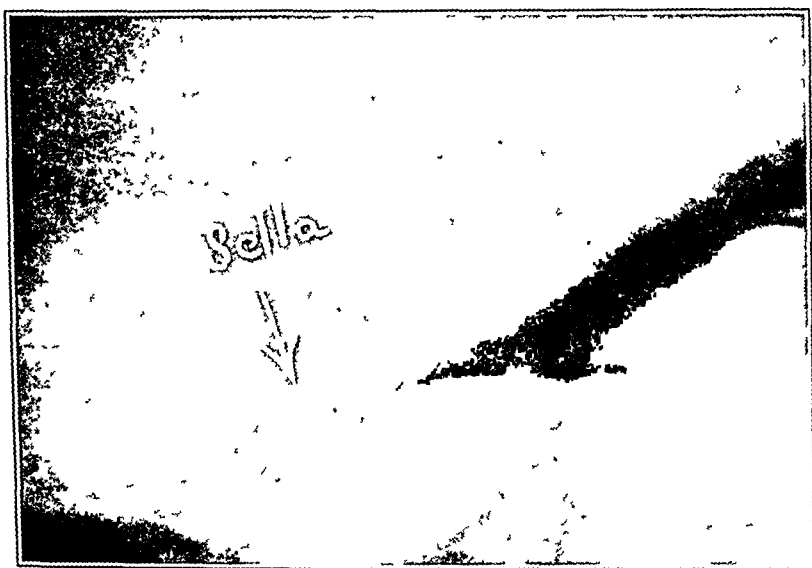


FIG. 2.—Case I, showing calcification in the pituitary region and confined to the pituitary region, occurring in an adult who showed relief of his clinical symptoms after the administration of pituitary extract.

farmer. He lived mostly in his library, being a student and author. Examination, in 1920, revealed a slender, graceful man weighing 140 pounds, 5 feet 8 inches in height. This weight never varied for many years. He exhibited no morphological abnormalities save that his hands were well shaped, fingers were long, thin and slenderly graceful; hair abundant; skin smooth and satiny. His finger nails exhibited none of the crescents at the base of the nails, an uncertain sign of pituitary dysfunction. His head was square, large, brachycephalic, index 82. At this time he suffered from nervous belching after food, rhinorrhea from the right nostril, depression, exhaustion and insomnia, all indications of a depressed pituitary function. There were no bladder symptoms, no polyuria or polydipsia. His heart and lungs were normal in every way; liver and spleen of

natural size; chest and abdomen well formed. There was no hint of Glenard's syndrome. There was slight arteriosclerosis. Blood-pressure was very low, being 110 systolic and 70 diastolic. A very significant sign of pituitary dysfunction was the fluctuating blood-pressure. It varied very much while being taken. It was indeed hard to obtain a constant reading. Nothing was found wrong with the nervous system save the vagotonia and neurasthenia above noted. Examination of his eyes by Dr. J. T. Carpenter revealed nothing abnormal in any way. Upon the supposition that he was suffering from pituitary hypofunction, his sugar tolerance was tested and found high; 300 gm. of glucose ingested caused no sugar to appear in the urine. Otherwise the urine was found to be normal. He was put upon 2 grains of the whole extract of pituitary three times a day. This at once began to act as a most beneficent hormone. Euphoria supplanted fatigue symptoms and depression, a condition that he had not known for years. His blood-pressure was not raised, so the change in his mental condition was not caused by this effect. His insomnia at once left him. He slept for hours during the day, and so soundly at night that he feared some sort of coma which alarmed him. Partial insomnia with excitability of mind followed this. His mental tone increased. He was able to work longer at his literary labors. Nervous depression disappeared, but as yet there was no increase in blood-pressure. The dose of the extract was then cut to 1 grain and the improvement continued. The drug "stimulated everything," to use the patient's expression.

*The roentgen-ray examination* of the skull at this time revealed normal sinuses, a small shallow sella turcica with the anterior clinoidals obscured and the fossa almost completely closed by either a prolonged clinoidal process or else by what might be called an operculum. To this restricted condition of the pituitary Timme ascribes the headaches that torment the victims of some forms of pituitary disease. Throughout, the gland shows a granular and cloudy condition in the radiographs, evidently due to deposits of calcareous matter. This latter infiltration being more intense in the posterior portion, the sugar tolerance being high and the vasomotor tone being low, the use of the whole gland extract was abandoned and  $\frac{1}{10}$  grain of the posterior extract was given, with excellent results. Later 1 grain of the anterior portion was added. After six months the weight had increased from 140 to 156 pounds, the constipation which he had had for many years disappeared and the blood-pressure rose from 110 to 138, but the varied readings noted during the observation still indicated some vasomotor imbalance. In this case Sergeant's white line was not elicited. The arrangement of the pubic hair is normal for a male. He is compelled still to take his pituitary extracts. Later when fatigue symptoms increased,  $\frac{1}{20}$  grain doses of thyroid extract were added to his other medicines with marked benefit. Iodides were too found beneficial.

*Remarks.* The frequent colds to which the patient was subject when a child may have caused a sphenoiditis. By continuity the inflammation may have spread by way of the sella turcica to the pituitary, giving rise to an inflammation therein. The ablation of the clinoids is significant of an inflammatory process. The sphenoid today is healthy. Timme has seen gross evidence of involvement of the pituitary fossa by sphenoid disease. He holds that the discharge comes from Rathke's pouch in the pituitary. The fatigue, depression, vagotonia, headache, lethargy, high sugar tolerance, low pressure, vasomotor instability, rhinorrhea, belching, absence of nail crescents, together with the radiograph showing the shallow sella turcica with clouding and granulation of the pituitary, constituted a syndrome that can be none other than hypopituitarism with calcareous infiltration. The gland extract feeding results confirm the dyspituitarism at least. This case suggested the review of other cases in our collection.

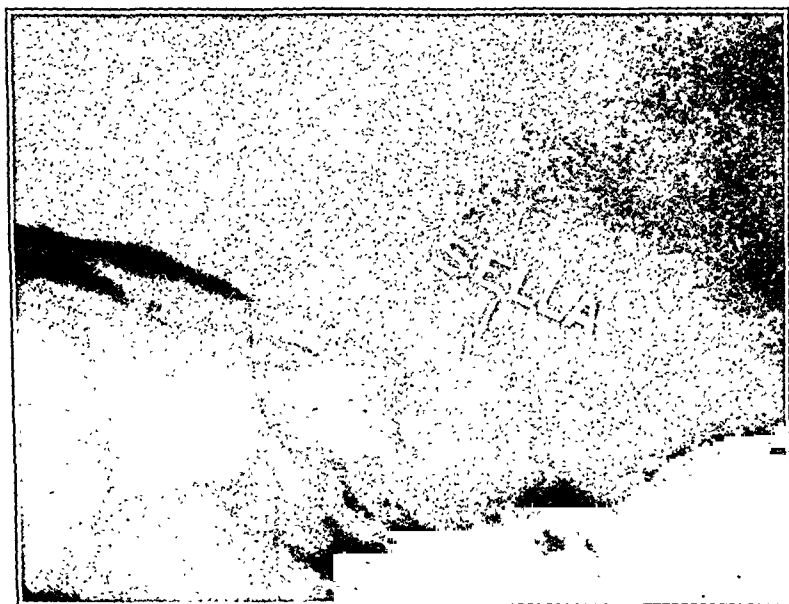


FIG. 3.—Case II, aged thirty-eight years. A case of hereditary optic atrophy previously reported by Zentmayer showing some evidence of calcification of the pituitary associated with enlargement of the sella and presenting evidence of mental deficiency. No improvement under pituitary feeding.

CASE II (Fig. 3).—Joseph C., aged thirty-eight years, a molder by trade, was sent to Dr. Pfahler for roentgen-ray study by Dr. Thorington in May, 1913. The patient then was nearly blind. He could find his way about and could just distinguish light from dark. He made a living by picking up waste paper in his town. When seen again by us eight years after, in 1921, an examination showed a small muscular man with the skull and facies of a moron. He presented none of the morphological changes of pituitary dys-

function. He was not neurasthenic. His family history is important in one respect in that his younger brother exhibited the same symptoms in a lesser degree. The history of both appeared in a paper by Dr. Zentmayer. Both were victims of Leber's disease (hereditary optic atrophy). The brother, Charles, died in 1918 of influenza. Other than this there was no history of blindness or mental deficiency in the family. He is married and has one child, which is healthy and strong. His previous medical history is unimportant. He never had syphilis but had suffered from quinsy and whooping-cough. He was hit on the head by a chain two years before he began to go blind. In 1912 he became partly blind in one eye. The first symptoms were visual disturbances like falling snow before his eyes, giving way later to fog. Six months later the other eye became affected. About this time he had a severe pain in his head which was hard to endure. Physical examination at this time revealed to us a rather small man of thirty-nine years weighing 133 pounds. All his thoracic and abdominal organs were normal in every way. His blood-pressure (recumbent) was 92 systolic and 65 diastolic. Sexual organs were normal in form, function, etc. Pubic hair was abundant and normal in distribution, and not feminine (which characterizes the pubic hair in male pituitary cases). His knee-jerks were prompt, his station normal, the pupils were large and reacted to light sluggishly. His speech was hesitating; his lips trembled before he spoke. His ideas were primitive. He had the mental status of a child of ten years. His skull was small, measuring  $18.5 \times 15$  cm. index 81. He had short spade-like hands with stumpy fingers. His appetite was normal. He did not crave carbohydrates abnormally; had no flatulency; slept well but had nocturnal polyuria, and was not easily fatigued. His vasomotor tone was fair. The urine was normal save for a low specific gravity. He exhibited a high tolerance for sugar (250 gm. of glucose ingested did not cause glycosuria). He did not exhibit Sergeant's white line of adrenal insufficiency; the thyroid was not palpable; the skin was smooth; chest very hairy (hypertrichosis). Eye examination by Dr. Zentmayer in November, 1917, showed vision: right eye,  $\frac{1}{180}$ ; left eye,  $\frac{1}{240}$ ; never any diplopia; absolute central scotoma 20 degrees in both eyes. Optic nerves then were greenish-gray and the vessels were contracted. In examination in 1921 he says that he saw red at times but not blue. Cushing says that color perception in these cases disappears before form perception. A roentgen-ray study by Pancoast, in 1912, then showed a sella turcica 13 mm. long  $\times$  12 mm. deep (a fairly large sella). The radiograph by Pfahler made in 1913 showed also some calcification of the pituitary, which had increased perceptibly when reexamined January 21, 1921, at which time the sella measured 14 mm.  $\times$  12 mm. That this man had hypopituitarism is shown by the high sugar tolerance and the low

blood-pressure in spite of an enlarged pituitary. Pituitary feeding (whole gland) in doses of 6 grams *per diem* caused no improvement in his condition. Thyroid added to this after three months also was followed by no improvement. The blood-sugar content was not estimated. Cushing's thermic reaction was negative. An examination of the sella turcica of a brother, Charles C., by Pancoast, in 1911, showed a trifling enlargement of the sella. Viewing the radiograph Pfahler is inclined to think that his pituitary also shows increased opacity, presumably due to calcareous deposit. In this case the pituitary enlarged to compensate for other endocrine default.



FIG. 4.—Case III, aged twenty-seven years, showing calcification in the sella with decrease in the size of the sella. Patient suffered from seven years from vertigo and vomiting.

CASE III (Fig. 4).—Miss E. F., aged twenty-seven years, referred to Dr. Pfahler for examination November 14, 1917, by Dr. William Menah. She had suffered from attacks of vertigo for seven years. Dr. Menah had treated the right ear for deafness. She also suffered from vomiting and the vomiting was associated with attacks of vertigo. The roentgen-ray examination of the head showed some calcification in the region of the pituitary. The anterior and posterior clinoid processes apparently met. The sella was abnormally small. In addition to this there was abnormal enlargement of the veins in the right parietal region. Enlargement of the veins



is at times associated with brain tumors in the region of this enlargement. Attempt has been made to trace this patient, but without success.

CASE IV (Fig. 5).—Miss M. S. M., aged nineteen years, was referred to Dr. Pfahler for examination of the head December 10, 1913, by Dr. Ralph Spangler. The patient had epilepsy since ten years of age. Menstruation began at thirteen. She had had five attacks of status epilepticus. Just previous to the examination she had gone through sixty attacks of epilepsy in nine days. Roentgen-ray examination of the sella turcica showed it to be about one-third normal size. The pituitary region seemed to be almost completely calcified. She died about six months later in status epilepticus. No autopsy was performed and none of the studies were made that we now make with reference to the pituitary.



FIG. 5.—Case IV, aged nineteen years. Patient suffered from epilepsy since ten years of age. Had several attacks of status epilepticus and died in this condition.

CASE V (Fig. 6).—Mr. R. D., aged twenty-two years, was referred to Dr. Pfahler May 7, 1914, by Dr. William E. Robertson for an examination of the skull, with special reference to the sella turcica. Dr. Robertson considered this case a typical Froelich type of hypopituitarism. He weighed 237 pounds, was about 5 feet 8 inches in height and had no pubic hair. The roentgen-ray examination showed calcification of the pituitary region with a very indefinite outline of the anterior and posterior border of the sella because of this calcification. It seemed, however, to be abnormally small. This patient was later referred to a sanitarium and died about four years ago. It would seem that with the definite diagnosis made by Dr. Robertson that these roentgen-ray findings would correspond very closely to that of hypopituitarism.

CASE VI (Fig. 7).—Mr. S. Y., aged forty-four years, referred to Dr. Pfahler by Dr. L. Webster Fox for roentgen-ray examination of the head on May 10, 1913, with a provisional diagnosis of tumor

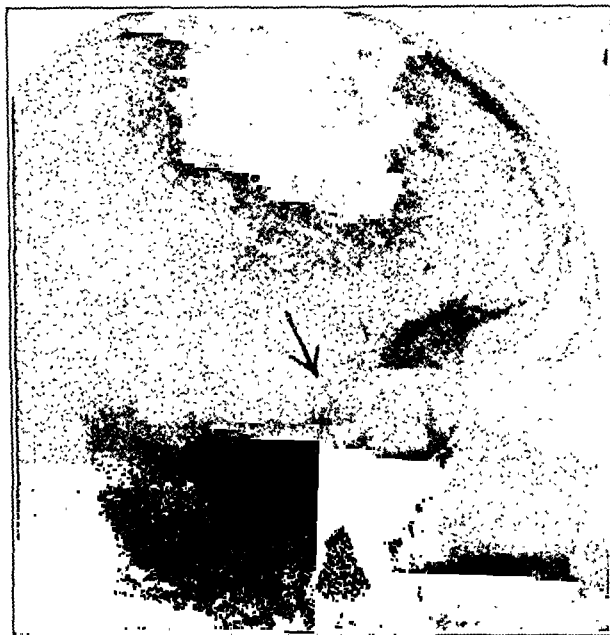


FIG. 6.—Case V, aged twenty-two years, showing calcification which is almost complete of the pituitary in a case of the Froelich type of hypopituitarism.

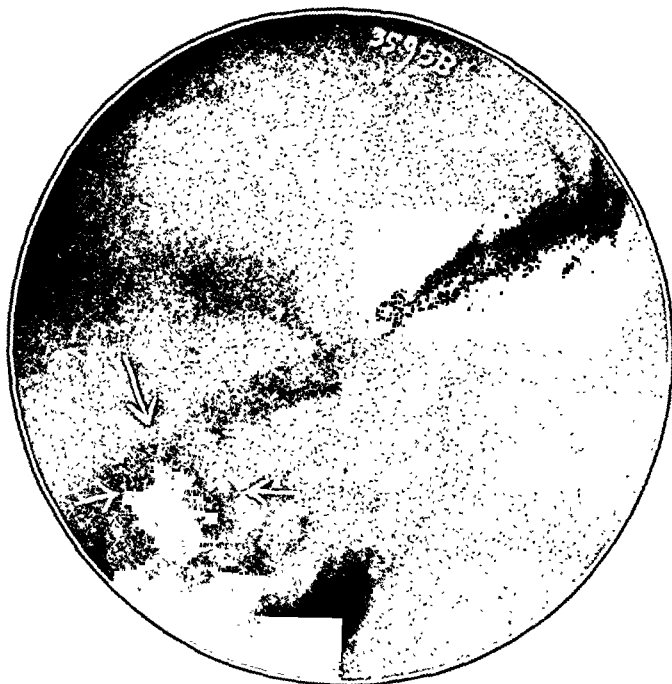


FIG. 7.—Case VI, aged forty-four years, showing almost complete calcification of the pituitary which is as dense as any part of the neighboring bone. Patient had double optic neuritis.

of the brain. Ophthalmological examination by Dr. Fox showed optic neuritis. Blood-pressure May 10, 1913: systolic, 165; diastolic, 132. Blood examination showed red corpuscles, 4,980,000; hemoglobin, 90 per cent; leukocytes, 10,000. Urinalysis negative. Roentgen-ray examination of the head showed an abnormal capacity in the sella turcica, evidently due to calcareous infiltration. The sella itself measured 12 mm. in the antero-posterior diameter and 10 mm. in the vertical. The floor of the sella was preserved. The anterior and posterior clinoid processes were obscured by the dense shadow in the pituitary region. The sphenoid sinus was clear. A communication from Dr. Fox June 1, 1921, is as follows: "Gradual loss of vision for the last six months (date of visit May 15, 1913), commencing in the right eye and extending to the left. Ophthalmoscope shows double optic neuritis, 5 to 8 diopters in height. Advised physician to give large and increasing doses of potassium iodide. May 25, 1913 he wrote me a letter stating that there was improvement in his condition. He could see more plainly. Have heard nothing since that date."



FIG. 8.—Case VII, aged twenty-six years, with the clinical symptoms of neurasthenia present. Calcified body located about 1 cm. above the sella turcica similar in appearance to the case reported by Duffy.

CASE VII (Fig. 8).—Mrs. A. H., aged twenty-six years, was referred to Dr. Pfahler for roentgen-ray study February 29, 1919, by Dr. Samuel Sica. Briefly her history referable to the conditions

in her head consisted in a statement that during three years she had had severe pains in the back of the neck and top of the head. Examination of the eyes by Dr. Zentmayer was reported negative. Two neurologists made a diagnosis of neurasthenia. An examination of the teeth resulted in the removal of a bridge and one tooth, but was not followed by any relief. The tonsils were removed but gave no relief. Headache was constant but worse at the menstrual period. Did not menstruate excessively. Headaches improved after the menstruation had started. An examination of the head showed especially obliteration of the diploë in the parietal region where the bone was very thick. In addition to this there was found a similar dense body, undoubtedly of calcareous

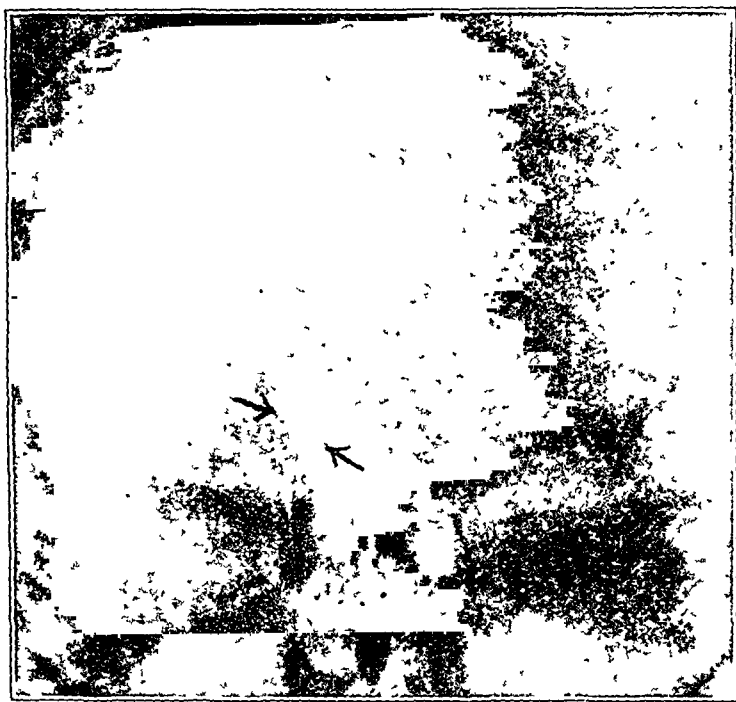


FIG. 9.—Case VII, showing the posterior-anterior view of this calcified body.

material, about the size of a pea, located just above the right side of the sella turcica, evidently in the region of the infundibulum. This location corresponds to the location of the calcareous material shown in the case reported by Dr. Duffy, previously referred to. Up to the present time there has been neither operation nor autopsy, and the exact nature of this case has not been determined.

CASE VIII.—Mrs. M. T., aged forty-six years, was referred to Dr. Pfahler for roentgen-ray study on February 11, 1916, by Dr. A. C. Morgan. The chief complaint was neuralgia affecting the left side of the head and the left side of the body, including the arm. At times there were also pains in the right shoulder and arm.

Removal of infected teeth had no affect on these pains. Roentgen-ray examination showed the accessory sinuses normal. The teeth were normal and examination of the cranium showed a calcareous deposit about the pituitary region with destruction of the anterior and posterior clinoid processes, and then above and posterior to this a marked decrease in the density. In addition to this there was an increased area of density over the Rolandic region on the left side covering an area about two inches in diameter. An attempt has been made to obtain the subsequent history in this case, but so far without success.



FIG. 10.—Case VIII, aged forty-eight years, showing calcification in the sella probably result of tumor formation.

CASE IX.—Mr. L. D., aged fifty-one years, a large man of normal configuration, weighing over 190 pounds, came to our attention in 1921 complaining of early fatigue and some psychasthenia. In 1912 and 1917 he broke down nervously and relinquished work for a time. His family history was not good, his parents both being nervous and his sisters likewise were afflicted. One sister had Graves's disease; his mother died of diabetes and the father of cancer. In childhood he contracted typhoid and had the milder childhood diseases. In early manhood he contracted diphtheria. He never had syphilis. Wassermann was negative on two occasions. Physical examination revealed nothing of importance. All of his organs were normal in function. A slight mitral murmur was heard at the apex of the heart, which was otherwise normal. Its rhythm was normal, although at times he experienced extra-

systoles and it was not enlarged. There was no dyspnea. (Earlier in life he was rather athletic.) Urine and blood were normal. There were no morphological abnormalities or skin changes suggesting pituitary dysfunction. Sergeant's white line was not discernible; thyroid not palpable; skin smooth; blood-pressure, 140; systolic reflexes prompt; station good; pupils normal. His head measured 21 cm. x  $16\frac{1}{2}$ ; index, 81. He has a moderate arteriosclerosis. Some tortuosity of the vessels in the retina were reported, but no other eye changes. A roentgen-ray study of his skull revealed an interesting condition. The sinuses were normal. The sella turcica was shallow, measuring 10 mm. in length by 7 mm. in depth. The pituitary was completely invested by a capsule. In order for the capsule to be demonstrable in the roentgenogram it must contain lime salts. There was no evidence of calcareous involvement of

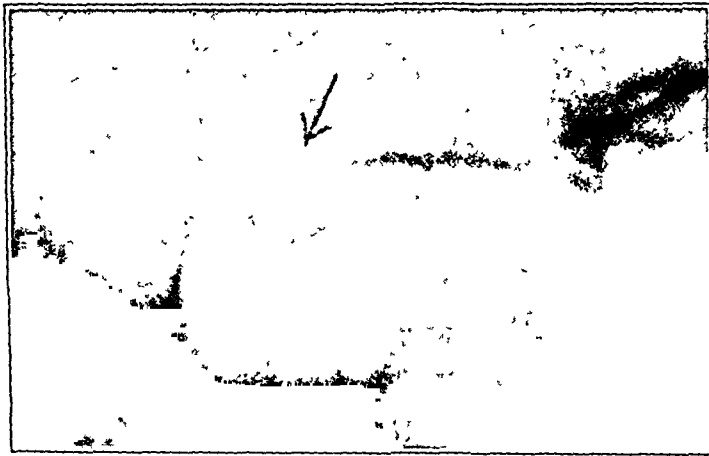


FIG. 11.—Case IX, aged 51 years, showing calcification of the capsule extending across the top of the pituitary area in a patient who had suffered from symptoms of neurasthenia, which was relieved by the administration of pituitary extract.

the gland itself. While there was no definite evidence of pituitary disease the vagotonia and neurasthenia improved under pituitary feeding. The enveloping capsule, which is demonstrated in the roentgenogram, is the only one of our series exhibiting this condition. Dr. Pfahler is of the opinion that the pituitary in this man is too small, being as noted rather shallow. His head is broad, however, and the interpupillary space much larger than normal. It is probable that the pituitary gland is wider than normal, making up for the deficiency in depth.

**Remarks on the Roentgenologic Findings.** Roentgenologists have been giving more and more attention to the size and shape of the sella turcica and to the clinoid processes in their relation to pituitary disease. It seems that we must now go a step further and pay close attention to the density of this area as compared

with the immediate surrounding brain structure. If the pituitary is not calcareous there should be no difference in the density of this area within the sella turcica from that of the surrounding brain tissue. Calcareous deposits within this area will indicate a diminution in the total value of the pituitary just as much as if the area were compressed by a small sella. Besides this we believe such infiltration is a definite indication of disease either present or past within the gland, though some studies suggested by this paper, now being carried on by Pfahler, would seem to indicate that calcareous deposits may be present or at least the gland may be more dense in patients who have no definite symptoms. It is always advisable to make stereoscopic studies of the sella before making a diagnosis.

Calcareous deposit is recognizable in the cases which we are reporting. In all but one of them there were definite clinical symptoms pointing toward pituitary disease. In one of these cases, also previously studied by Drs. Pancoast<sup>9</sup> and Zentmayer,<sup>10</sup> there was no calcareous deposit reported in the examination made a year previously, but a study of the illustrations in two different publications would seem to indicate that this area is more dense than that shown in the other illustrations, and we would assume that there were some abnormal calcareous deposits at that time, though it had undoubtedly increased within the year. In addition to this, Pancoast has referred to Pollock's paper,<sup>11</sup> in which there was reported another case of hereditary optic atrophy in which there was found a shadow about the size of a very small bean with a concavity downward and situated in and a little below the center of the pituitary fossa. Presumably this was calcareous deposit. In addition to these 9 cases of calcification in the region of the pituitary reported by us, and in which there was associated more or less evidence of hypopituitarism, Dr. Pfahler has in his collection 4 cases, the histories of which are not included in this paper, and in which there is lime deposit in the pituitary area, though the patients are suffering from acromegaly.

The observations made in this paper have suggested to Dr. Pfahler the importance of studying the normal sella turcica, and to this end he has made, up to the present time, 75 such studies in patients who had no evident pituitary symptoms. In this number there has been demonstrated some evidence of calcification in 4 cases, or 5.4 per cent. We believe that it is possible for the other endocrine glands to compensate in part, for a time at least, for the defective function of this gland, and this might explain the absence of symptoms at present which in later years may become

<sup>9</sup> Pancoast: *Am. Jour. Roentgenol.*, January, 1919, No. 1, 6.

<sup>10</sup> Zentmayer: *Concerning the Etiology of Hereditary Optic Atrophy*, Report of Two Cases, *Arch. Oph.*, 1918, No. 16, 47.

<sup>11</sup> *Loc. cit.*

manifest, for it is well known that pituitary changes are often very slow. Even with normal-sized sella turcica and normal clinoid processes, calcareous infiltration in this gland might account for diminished endocrine function. Even if no symptoms are present any such finding should raise the suspicion of dysfunction and the patient should be kept under observation at intervals over a long period of time for any calcification developing in soft tissues is evidence of tissue death. At times such deposit may indicate the formation of a neoplasm.

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## ACTINOMYCOSIS OF THE TONGUE.

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ACTINOMYCOSIS is common among cattle and hogs. It occurs quite frequently in man, although often it is not recognized, especially around the head and neck. One hundred and twenty-seven patients with actinomycosis were examined in the Mayo Clinic from January 1, 1910, to January 1, 1921. In 66 the disease occurred in the head and neck; in only 3 did it occur primarily in the tongue.

In 1826, Leblanc gave a careful description of a disease affecting the jaws of cattle which he called "osteosarcoma." In 1845 von Langenbeck first noticed the characteristic yellow granules in a case of caries of the spine in man. Bollinger (1877), however, very largely deserves the credit for the recognition of the disease as a pathological entity. He first ascribed the peculiar enlargement of the jaws of cattle, popularly known as "lumpy jaw," to the organism that Harz had just named the "ray fungus," or "actinomyces." Israel, in 1878, recognized the organism as the cause of the disease in man. Since that time much has been written on the subject and descriptions of this condition in practically every organ and tissue of the body have been recorded.

Actinomycosis rarely occurs primarily in the tongue. It may occur in this location by metastasis or by direct extension from involved contiguous structures. Illich, in 1892, found only 15 in 569 cases in which the growth originated in the tongue. Ruhräh, in 1899, collected 1094 cases of actinomycosis from the literature. Krymow, ten years later, was able to find only 27 cases in which the tongue was primarily involved. Von Baracz reported 3 of this



type in a series of 52 cases of infections in the head and neck. Schlangé reports only 1 such case in a total of 60 general infections.

Undoubtedly the tongue is more often involved than these data indicate. Three cases have been seen in the Mayo Clinic since October, 1919; none had been recorded previous to that time, and thorough microscopical examination of all specimens of inflammatory tumors of the tongue in the Mayo Clinic museum did not reveal another case. Such examination is not necessarily final, since it was not possible to study the pus contained within the nodules. Four hundred and thirty-seven tumors of the tongue, of all types, have been examined in the Mayo Clinic. Of these, 300 were malignant, 100 benign, and 37 inflammatory, so that the 3 cases of actinomycosis of the tongue formed 0.7 per cent of the entire number.

The actinomycotic or so-called wooden-tongue of cattle is of comparatively frequent occurrence. Claus estimates the incidence of this type of lesion as 29 per cent of all actinomycotic infections in cattle and Leclerc as 18 per cent. Von Hollandt notes that in at least 5 per cent of the tongues of slaughtered hogs definite, encapsulated, actinomycotic nodules can be demonstrated. The rarity of the infection of this organ in man has been explained by Poncet and Berard as owing to the fact that the tongue consists of muscle-bundles richly supplied with bloodvessels and protected with a thick epithelial covering. Since the structure of this organ in animals is practically the same as in man the explanation is hardly sufficient. It seems more logical to attribute the relatively more frequent occurrence in animals to the fact that their habits and mode of life bring them in more direct contact with infectious material. It is conceded that most infections due to actinomyces are of vegetable origin, such as the various grasses and grains; barley beards are supposedly the most common cause. Von Hofman and Bostroem have shown that the ray fungus is an almost constant finding on the grain beards in the tonsillar crypts of slaughtered hogs. Von Hollandt, who has conducted an excellent investigation in the slaughter houses of Dresden to ascertain the frequency of infection of the tongue in supposedly healthy hogs states that at least 73 per cent are due to infected plant particles.

Bostroem, who studied serial sections of primary actinomycotic tongues of cattle, was able to demonstrate foreign bodies in nearly all recent cases. The presence of such foreign bodies has also been shown in the primary lingual nodules in man by Fischer, Jurinka, von Baracz, Harms, and Kockel. It is readily understood how these spore-bearing particles when thrust through the mucous membrane of the tongue can find a favorable medium in which the anaërobic fungus may proliferate. That foreign bodies are not the only source of infection is quite evident, however, since the fungus has been

demonstrated in a number of instances in the cavities of carious teeth in healthy persons, and trauma to the organ by such teeth with subsequent infection is highly probable.

In reviewing the literature we found records of 35 cases of primary actinomycosis of the tongue; our 3 cases made a total of 38. Twenty-seven of the series were in males and 10 were in females; the sex was not given in 1 case. The disease occurs in adults; only 1 case has been reported in a patient under twenty, a young man of eighteen.

Incidence of the disease by decades according to ages:

Age.	Cases.
18 years . . . . .	1
21 to 30 " . . . . .	8
31 to 40 " . . . . .	6
41 to 50 " . . . . .	9
51 to 60 " . . . . .	5
61 and over . . . . .	4

The condition is more commonly found in farmers or in persons whose rural life exposes them to infection. The disease cannot be said to be occupational since, besides farmers and their co-workers, a physician, an office girl, a janitor, a cabinetmaker, two merchants, a naval pensioner, a stonemason, and a judge are noted in the series. One of the patients seen in the Clinic, a judge, mentioned a habit of chewing bits of grass while he played golf. The occupation of 28 patients was recorded. Fifteen (53 + per cent) were connected with rural life, 13 (46 + per cent) were patients not connected with rural life.

The clinical history of actinomycosis of the tongue varies in different cases. The patient usually has a single, isolated nodule in the anterior half of the tongue, often near the tip, varying from 1 cm. to 1.5 cm. in diameter. This location is significant, since in giving a history the patient often mentions injury to the tongue by the teeth or some foreign body. The condition may be acute in onset, with severe pain, throbbing, local tenderness, general malaise and an elevation of temperature, as in abscess of the tongue. It may develop insidiously during the course of several months or even three or four years. Without secondary infection the process is usually slow to develop. Enlargement of the regional lymph nodes has often been observed, but only staphylococci, never actinomyces, have been found in these, and the adenitis subsides with the clearing of the local condition of the tongue.

**Diagnosis.** The diagnosis must be based on the clinical picture and confirmed by microscopical examination. Aspiration of the contents of the suppurating nodule is usually unsatisfactory; it is best to excise the entire nodule for diagnosis. Often only a few of the characteristic granules necessary for a positive diagnosis may be present within the nodule, and unless these granules are secured in

the small specimen removed for microscopic examination it is impossible to make a diagnosis. Grossly the lesion must be distinguished from tertiary syphilis, tuberculosis, epithelioma, inflammatory cyst, and fibroma. One of our patients was referred with a diagnosis of probable malignancy. One patient was believed to have an inflammatory nodule and the third a simple infected cyst.

**Pathology.** A small isolated nodule, varying in size from 0.6 cm. to 3 cm., and enclosed in a fibrous capsule, will usually be found near the dorsum unless the entire thickness of the tongue is involved. The nodule often becomes infected secondarily with the formation of a small encapsulated abscess. This may rupture spontaneously or in rare instances a diffuse lingual abscess may form. Baracz's third case was of the latter type.

The overlying mucous membrane varies in appearance with the stage of the process and consequently may be normal, yellowish or elevated and tense, as though covering a superficial cyst or a small abscess about to rupture. It rarely ulcerates. Some writers mention a peculiar bluish-red discoloration as decidedly suggestive of actinomycosis in this location, but this was not seen in our cases. The usual picture of a diffuse, indefinitely outlined induration with multiple sinuses, which depend on the ramifying granulation tissue tracts extending into the adjacent normal tissue, is rarely seen in the tongue; it was seen in only 1 case in the series, that of Fischer.

Most observers agree that no suppurative process is characteristic of actinomycosis and that suppuration is always the result of secondary infection usually due to the staphylococcus.

**Treatment.** The condition is treated medically and surgically. Arsenic has been used and believed to be of some therapeutic value, but its action is probably due to its systemic effect. Injections into the tongue of various antiseptics and germicides, such as bichloride of mercury, tincture of iodine, and zinc chloride, have been made with definite improvement, but such methods seem hazardous. The nodules have been known to disappear by the use of large doses of potassium iodide internally (Claisse). Poncet and Berard, however, concluded that incision or spontaneous rupture of the abscess in conjunction with the potassium iodide internally produced much more rapid and satisfactory results. Surgical treatment alone, or combined with the medical treatment, seems to be the rational procedure. Wide excision with primary suture of the wound was done in our cases and is the treatment of choice if a discrete, isolated nodule is present. If the abscess is too large for excision, drainage with or without curettement is advisable. Daily swabbing of the wound with tincture of iodine, packing with iodoform gauze, the administration of large doses of potassium iodide, and the use of radium as employed in the Mayo Clinic in all cases of actinomycosis of the head and neck are unquestionably of distinct benefit.

**Prognosis.** The prognosis varies with the stage of the process and the clinical picture at the time of the patient's examination. It is favorable in those cases in which a small nodule is situated well forward near the tip of the tongue: less favorable in those in which there is a diffuse area, especially if it is near the base of the tongue or if there is a definite abscess.

Death has been reported in 1 case (Mayer's) from multiple abscesses around the lower jaw, neck, and upper chest one and one-half years after excision of the primary nodule near the tip of the tongue. The abscesses were probably due to metastasis from the primary focus.

**Case Reports.** CASE I (292538).—Mrs. S., aged sixty-three years, wife of an implement dealer, came to the Clinic October 9, 1919, because of a small nodule on the tip of the tongue which had been present for two months. The nodule had been incised by her home physician one week before and a small amount of pus evacuated.

Examination showed a small, hard, whitish nodule about 0.63 cm. in diameter on the dorsum of the tongue just back of the tip. Slight induration extended down into the tongue. The nodule was excised under local anesthesia and on microscopic examination was shown to be actinomycosis. Fourteen months later there was no recurrence.

CASE II (265308).—Judge F., aged fifty years, came to the Clinic September 17, 1920, complaining of a small nodule in his tongue. Four weeks before he had noticed a burning sensation on the dorsum of the tongue, which he thought was due to heavy pipe smoking. Five days before coming to the Clinic he discovered a small nodule in his tongue. He consulted two physicians, who thought that it was probably malignant.

Examination revealed an indurated nodule, only slightly tender and freely movable, 1.25 cm. in diameter, just to the right of the midline of the dorsum of the tongue and about 3.75 cm. back of the tip. The nodule was believed to be inflammatory and excision for definite diagnosis was recommended. Actinomycosis was diagnosed. The patient was given large doses of potassium iodide. He has not had a recurrence.

CASE III (339709).—Mr. M., aged forty-six years, meat cutter, was examined in the Clinic November 3, 1920. He complained of many symptoms, most of which were apparently functional, following the nervous shock incident to the death of his son seven years before. He was referred to the Section on Laryngology, Oral and Plastic Surgery for examination because of a small nodule on his tongue which had appeared a week or ten days before.

TABULATION OF CASES

No.	Author, Date.	Sex, Age.	Occupation.	Etiologic factors.	Location of lesion. Symptoms. Duration.	Diagnosis.		Operative findings. Treatment.	Result.
						Clin- ical.	Micro- scopic.		
1	Hacker 1885	M 30	.....	Patient had opened "actino" abscess on jaw of cow two months before	Tip	+	....	Excision	
2	Hochenegg 1886	M	Son of farmer	Patient accustomed to chewing grain during harvest	Right anterior quadrant	+	....	Excision	
3	Meyer 1887	M	Farm hand	....	Middle, near tip	+	....	Incision and curettement (rapid local healing)	Death from multiple ab- scesses of jaw, neck and chest 1 1/2 years later. ?
4	Santer 1888	M 50	.....	....	....	+	....	Excision; suture	No recurrence.
5	Santer 1888	M 50	Gentleman	....	Right anterior quadrant 1 week	+	....	Excision; suture	No recurrence.
6	Ullmann 1888	F 56	Wife of field worker	....	Dorsum 1 cm. from tip	+	....	Nodule size of "hazel- nut," mucous mem- brane violet; excision; sutured	No recurrence.
7	Ullmann 1888	M 54	Farmer	....	Right anterior quadrant 4 weeks	+	....	Hard nodule size of "grape," mucosa nor- mal; primary ligation of lingual artery; excision of one-half of tongue	No recurrence.
8	Maydl 1889	M 48	Physician	Moistened finger with tongue while inspecting meat	Middle, 3 cm. from tip; pain; patient sick 2 mos.	+	....	Softened area in middle of tongue; drainage of abscess; excision of walls; suture	No recurrence.
9	Kubaeki 1889	M 35	Farmer	....	Right anterior quadrant; pain 14 days	+	....	Hard nodule size of "cherry," excision; suture	No recurrence.
10	Zühls 1889	M 56	Forester	....	Recurrence in right anterior quadrant, 3 or 4 weeks; re- currence after 4 mos.	+	....	Nodule size of "hen's egg," incision twice; recur- rence 4 months later; drainage; curettement	Recurrence; no recurrence.
11	Zühls	F old	....	....	1 week	+	....	Incision	No recurrence.

12	Schertau 1890	M 24	Field worker	Rye beard in tongue while threshing	Right anterior quadrant, 14 days	....	+	Nodule size of "pea," grain beard covered with actinomycetes; inci- sion; curettement.	No recurrence.
13	Baracz 1890	F 22	Office girl	....	Left tip; patient sick 3 mos.	....	+	Round, elastic nodule size of "pea," incision; curettement	No recurrence.
14	Fischer 1890	M 29	Fieldworker	Barley beard in tongue while threshing	8 days	....	+	Soft, fluctuant nodule size of "small nut," grain beard with fungi growing about it; inci- sion; curettement.	No recurrence.
15	Illich 1892	M 75	Janitor	....	Dorsum 1 cm. from tip; sick 2 mos.	+	....	Hard nodule size of "pea"; incision; curettement	No recurrence.
16	Illich 1892	M 36	Cabinet- maker	Soreness caused by pipe stem often noticed	Right half; soreness 3 weeks	+	....	Hard nodule; incision; curettement	No recurrence.
17	Schlange 1892	..	....	....	Middle of dorsum	?	....	Firm nodule size of "hazelnut," resembling gummas; incision; cu- rettement	No recurrence.
18	Jurinka 1895	M 46	Merchant	Accustomed to chewing grain	Left half; pain; ten- derness; indura- tion for 3 months ascribed to sting noted 2 years pre- viously	....	+	Nodule size of "cherry," cavity 3 mm. in diam- eter in center contain- ing five "actino" grain ules around a grain beard; incision; curette- ment.	Outcome un- certain.
19	Frey 1897	F 28	....	....	Midline of dorsum; region of circum- vallate papillae and forward; pain 4 years	+	....	Nodule size of "cherry," swelling in middle of tongue 3 cm. in diam- eter, covered with pap- illary growths; pus and granules; incision	No recurrence.
20	Frey 1897	M old	Fruit merchant	Tongue injured by fruit stone 3 wks. before	Left anterior quad- rant; pain	+	....	Hard nodule size of "nut," excision (local anesthesia)	No recurrence.
21	Chaisse 1897	M 39	....	Irritation from jagged, carious tooth produced ulceration	Right margin ante- riorly; ulceration healed following extraction of a tooth; nodule 3 months later; ab- scess several mos. later	....	+	Ulceration primarily a fluctuant nodule as re- currence; actinomycis- granule obtained on aspi- ration; process cleared under potassium iodide	No recurrence.

No.	Author, Date.	Sex, Age.	Occupation.	Etiologic factors.	Location of lesions. Symptoms. Duration.	Diagnosis.		Operative findings. Treatment.	Result.
						Clin- ical.	Micro- scopic.		
22	Cooper 1899	M '60	Naval pensioner	Habit of chewing straw	Midline of dorsum 1 inch from tip	....	..	Nodule size and shape of "almond," lesion thought to be malignant; ab- scess $\frac{1}{2}$ inch in diam- eter; granules; excision of tongue	No recurrence.
23	Ridger 1901	M 45	Farmer	....	Left side, pain; ab- scess developed and ruptured in 3 days; recurrence 4 years later and 4 years and 7 mos. later	....	+	Marked swelling; single abscess primarily; mul- tiple abscesses as recur- rence; actinomycos- found on second recur- rence; incision.	
24	Smirnow 1901	F 60	Farmer's wife	Sheared sheep hav- ing actinomycosis	7 months	....	+	Hard nodule size of "hazelnut," potassium iodide for 23 days with- out result; excision.	No recurrence.
25	Baracz 1902	F 32	Farmer's wife	Chewed wheat while threshing	Right posterior quadrant; dys- phagia; pain 3 weeks	....	+	Hard nodule size of "nut," grain beard; incision; curettement	No recurrence.
26	Baracz 1902	M 36	Farmer	....	Dysphagia; pain 1 week; recurrence 3 months later	....	+	Diffuse swelling; tongue twice normal size; fluc- tuant area; foreign body; pus with granules; inci- sion	One recurrence; patient lost sight of.
27	Kellock 1902	M 18	Stonemason	....	Right dorsum and margin; noticed for 2 days	....	....	Soft swelling size of "pea," numerous gran- ules; incision and cu- rettement; potassium iodide internally	Apparently no recurrence.
28	Schwiehorst 1903	M 27	Day laborer	....	Middle; dysphagia; pain 6 weeks	....	+	Nodule; no fluctuation; no foreign body; diag- nosis by aspiration; in- cision; curettement	No recurrence.
29	Juffinger 1905	F 34	...	Sensation as of fish- bone thrust into tongue while eat- ing 5 wks. before	Right margin oppo- site first molar; dysphagia; pain 5 or 6 weeks	..	+	Hard, red nodule 0.2 by 1.5 cm. with small ab- scess; pus with granules.	

30	Maier 1906	M 73	.....	Right half 6 weeks	....	+	Swelling; pus with granules; excision under local anesthesia	No recurrence.
31	Krymow 1908	M 48	Farmer	Left anterior quadrant; swelling; pain 6 weeks	....	+	Fluctuant nodule 2 cm. in diameter; pus with granules; incision and curettement.	No recurrence.
32	Krymow 1908	M 42	Artillerist	Right margin opposite inferior third molar; pain; abscess ruptured in 20 days; nodule appeared later	....	+	Hard nodule 1.5 cm. in diameter with fistulous opening in center; pus with granules; excision under chloroform	No recurrence.
33	Roth 1916	F 22	Wife of rancher	500 cattle graze about house during the summer	....	....	Recurring pustules with coalescence and ulceration; scrapings and culture showed actinomyces; removal of one-third of tongue and cauterization of area	No recurrence.
34	Harms 1920	F 65	.....	Dorsum near tip, 0.5 cm. from margin; tenderness; pain 14 days	....	+	Hard nodule size of "hazelnut," foreign body in center of abscess; splinter of wood; grain beard; excision with Y	No recurrence.
35	Kockel 1920	M 40	.....	Habit of chewing tooth picks	....	+	Abscess size of "pea" in center of inflammatory mass; small splinter of wood in abscess	No recurrence.
36	New	F 63	Wife of implement dealer	Dorsum, just back tip; itching sensation 2 months	....	+	Hard, whitish nodule 0.62 cm. in diameter; actinomycosis; excision under local anesthesia	No recurrence.
37	New	M 50	Judge	Habit of chewing grass while playing golf	....	+	Indurated nodule 1.87 cm. in diameter; actinomycosis; excision under local anesthesia	No recurrence.
38	New	M 46	Meat cutter	Middle, just to right of midline; slight tenderness; 10 days	....	+	Soft, fluctuant nodule 0.62 cm. in diameter; actinomycosis; excision under local anesthesia	No recurrence.



On examination a slightly tender, fluctuant nodule about 1.25 cm. in diameter was found on the left side of the dorsum of the tongue. The mucous membrane covering the nodule was slightly elevated and yellowish. A diagnosis of infected cyst was made and the lesion was excised under local anesthesia. Microscopical examination showed the condition to be actinomycosis. The patient was given large doses of potassium iodide.

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## PAIN IN THREATENED AND REAL GANGRENE OF THE EXTREMITIES: ITS RELIEF.

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IN no pathological condition does pain play a more important role than in gangrene of the extremities. One of the earliest diagnostic signs of a failing circulation, it influences the whole course of the disease by reason of the fact that upon its control, more than any other single factor, depends the success or failure of whatever form of treatment may be outlined. It follows, too, in consequence that in addition to its other qualities, pain in gangrene is of real prognostic importance.

The underlying condition in cases of threatened gangrene is a diminished blood supply. This may be manifested by an early numbness and tingling of the toes and feet and by blanching of the extremities, together with a cold feeling; or, the first complaint may be an inability to walk any great distance without resting at short intervals, so-called intermittent claudication. But whatever the early signs may be, in practically every instance a certain amount of pain is complained of in addition to the other symptoms noted. Indeed, so prominent is this feature that those who see most of the circulatory diseases of the extremity have come to feel that when a patient comes in complaining of pain in his limbs of such severity that it wakes him at up night, the condition is very likely to be associated with a diminution of the blood supply.

In some way this pain must be associated with the ischemia consequent upon blocking of the main vascular channels, but just why there should be pain at all I am at loss to say. It is

known that nerve tissue withstands ischemia less well than tissues of other types, so that one might think that the underlying cause of the pain is a nerve degeneration. As a matter of fact, circulatory deficiencies of the extremities are usually diagnosed at first as some form of neuritis, and it is only when the true state of affairs is discovered that the real malady becomes apparent. But while there may possibly be some low-grade inflammation around the nerves of the extremity affected, no one has thus far noted a real nerve degeneration such as might give rise to the pain so bitterly complained of by practically all patients who are threatened with gangrene of an extremity. The most that one can say is that in those extremities whose blood supply is diminished there is a pain that increases in direct ratio as the gangrene becomes more evident, and in just so far as one is able to combat successfully the encroachment of the gangrenous process will the pain be relieved. In other words, relief of pain in these conditions really amounts to improving the circulation to such extent that the gangrenous process is halted. This fact appears to discredit the nerve degeneration theory of the pain, since if a nerve is degenerated it is hardly likely that regeneration would come to pass immediately upon an improvement in circulation. Nerve regeneration ordinarily is a very slow process.

In almost every case of threatened gangrene the main vascular channels are occluded from one cause or another, at some point in their course, so that, for all practical purposes, measures of relief amount to developing an adequate collateral circulation. The only trouble is that the development of a collateral circulation sufficient to nourish the parts is a time-consuming procedure, and not only is it time-consuming, but it involves the use of certain forms of therapy which in themselves seem to give rise to more or less discomfort. Therefore, the pain element is of extreme importance because upon the patient's ability to withstand its ravages, frequently depends the success or failure of the whole treatment.

One might think that it would be a simple matter to give these patients sedatives of one kind or another and thus put them in position to stand almost any amount of pain; but experience has shown that this is all but impossible, because the pain is of such a character that unless huge doses of morphine are given little or no effect is seen, and everyone knows what large doses of morphine will do to a person when given over a long period of time. For the successful handling of cases of threatened gangrene occupies a period often of months and even years, so that if one is to have any success at all he had best beware of sedatives other than the milder ones, such as codeine and the bromides. Sodium bromide has been of great assistance, and when judiciously employed may be continued over an indefinite period of time.

Rest of course is of extreme importance, but here, again, one

is confronted with a situation that is unique to this condition—namely, a tendency upon the part of the patient to get up and walk about whenever his sufferings become acute. The whole picture, the whole conglomeration of features connected with extremity gangrene, differs vastly from any other surgical condition with which I am familiar. Ordinarily if one has pain he stays in bed; he takes a sedative or a hot-water bottle or something equally efficacious and awaits results. In this condition the patient seems unable to rest; it takes huge doses of sedatives to relieve him, and since it is impossible to continue this practice over long periods of time, he resorts to walking up and down his room until, thoroughly exhausted, he falls over into a troubled sleep.

Rest is important none the less. It is difficult to obtain at times, but much can be done by perseverance, especially if one can get his patient to the point where he will consent to remain in bed even if he has pain. To do this, one is at times forced to promise the patient that he will not be permitted to suffer too much, by which he will understand that morphine will be given if need be. This gives him something to hang to while it gives the surgeon an opportunity at least to start those measures of relief which have for their objective the development of a collateral circulation in the affected limb adequate to sustain tissue life. All of these measures have to do with contracting and dilating the larger and smaller bloodvessels—so called bloodvessel exercise—since it is felt that spastic contraction of terminal vessels accounts in no small degree for the diminished blood supply carried down the limb. It is either a spastic condition or a collapse of these vessels due to disuse, but in either case alternate contracting and dilating of them has been found beneficial in that it is easier for blood to circulate through them. The cause of this collapsed condition of the vessels at first sight seems to be due to the fact that with the main vessels occluded little if anything is going through them, so that it is only natural that they should be in a state of collapse. At the same time one must not lose sight of the fact that in general those who are suffering with threatened gangrene of an extremity, unless they have a generalized arteriosclerosis with a coincident nephritis, are usually found to have a distinctly lowered blood-pressure. So that in certain cases I am sure there is not sufficient force back of the blood stream to send it down the collateral channels as long as the smaller bloodvessels are in a state of either spasticity or collapse from disuse.

I usually start my patients off by having them give the affected part an alternate hot and cold plunge by means of two pails of water. One of these pails is filled with iced water while the other is filled with water almost at the boiling-point. The patient plunges his foot first into the cold water, leaves it there a second or two, and then without drying it at all, plunges it immediately

into the hot water. After it has been in that a few seconds he puts it back into the cold water and from there again into the hot water, continuing this alternate cold and hot plunge for about five minutes, finally ending up with the hot-water plunge. By this means his vessels alternately contract and dilate, and in many cases the process is quite obvious to the eye by the blanching and reddening of the skin of the affected part. The process is finished off with the vessels in dilatation. The patient is put through these exercises three times a day if he can stand it. Sometimes the patient is unable to stand this treatment at all, although, as a rule, he gets used to it and is able to go through the exercise without difficulty. In most of the cases that have been unable to stand it there has been some degree of ulceration either around the base of the nails or at some place on the foot. At the conclusion of the baths the foot is dried off thoroughly and the whole foot and leg are well oiled with any kind of oil, such as olive oil, cocoa butter, etc., particular attention being given the parts around each nail and between the toes. The patient is then instructed to lie down and keep the foot warm for at least an hour. It is not sufficient to carry out this exercise merely with the water in shallow pails; it is far better to have a deep bucket so that the whole leg can be put in the water almost up to the knee.

In between these baths I am in the habit of having the patient use an electric vibrator, such as is used by barbers for face and scalp massage. This is used over the entire leg and foot, the patient himself carrying it out. At first the skin is liable to be slightly irritated by the machine, but this very quickly wears off and the patient is able to use the vibrator for five or ten minutes four or five times a day, after each application the whole leg being anointed with oil. I lay great stress on this lubrication, not because of any inherent qualities in the oil itself, but because it is extremely important that the skin in these cases be kept in as healthy a condition as possible; and that all scratches, cracks and abrasions be studiously avoided, since only too frequently they are the starting-points of infections and ulcerations. By means of the baths and the use of the vibrator, together with rest and perhaps a small quantity of bromide, the acute condition is very frequently overcome so that it is possible to go a trifle more slowly. After two or three weeks of these frequent hot and cold baths I usually have the patients employ them only in the morning and in the evening, although they are encouraged to use the vibrator as often as they wish. This in my experience has been the great pain reliever, so that its use can be regarded as a sort of index as to the amount of pain the patient is suffering.

In addition to these measures of exercise I use one other, namely, that of occluding all the blood through the affected part by means of a bandage applied above the knee after the leg has been elevated

and all blood expressed out of it. This measure is carried out as follows: With the foot and leg slightly elevated a muslin bandage is applied, starting at the toes and running up with increasing pressure above the knee. At that point another bandage is placed around the leg in the form of a wide constricting bandage. This is left in place for about one minute, during which time the bandage that has been put on from the toes upward is released. At the conclusion of this time the constricting bandage is suddenly cut and the leg held down over the side of the bed. With the constricting bandage in place the leg will have a real cadaveric appearance, while as soon as it is cut there will be an immediate rush of blood toward the extremity, its progress being noted by the fiery red blush to the skin. If one carries out this procedure in both legs it will be found that blood flowing to the toes will occupy a period of from five to fifteen seconds in the healthy extremity, while it will take from thirty to sixty or even one hundred seconds or more in the affected extremity. This is sometimes called the reaction time of the bloodvessels, by which is meant the time it takes the blood to reach the terminal vessels. Naturally in states of threatened gangrene the blood is unable to get down to these terminal vessels rapidly; in other words, the reaction time is slowed. As the collateral circulation develops the reaction time is increased and tends to become normal. The method that has just been explained is that of Moskowicz, and in other conditions is used to determine the state of collateral circulation. I use it in these states of threatened gangrene because of my feeling that it helps to dilate the collapsed bloodvessels. I am accustomed to use it on all patients once a day, but here again there are limitations because of the pain it may occasion. If carefully carried out, however, there need not be any great amount of discomfort.

In addition to all these measures I have been accustomed to give all patients a course of Ringer's solution by means of the duodenal tube. Just why Ringer's solution should help in these conditions it is difficult to say, but for some years now it has been felt that by this means the viscosity of the blood could be lowered and that this was much to be desired. The fact remains that there has been a curious alleviation of pain in many of the cases coincident with the giving of Ringer's solution. Many of these individuals object to taking it by means of the duodenal tube, so they are permitted to drink it, but the solution has a definite salty taste and it is impossible to take it in great quantities or over a long period of time by mouth. Furthermore, it is possible that the character of the solution is changed by the gastric juices, so that it is much better to give it by means of the duodenal tube. Even by this means there comes a time when the patient is unable to continue the use of the solution; he feels nauseated and vomits.

This usually comes on after a two or three weeks' course, at which time it is best to discontinue its use for some weeks and later to resume it. The amounts given vary, but generally about one liter is given a day either at one sitting or at two. In certain cases as much as two or three liters have been given.

I have never had any great success with baking. On the contrary most of my patients have disliked it because they maintained it increased their pain—and this in spite of the fact that the measure has been instituted with care and they have not been subjected to specially high temperature. The various baking ovens have been used as well as electric-light ovens. Most of the patients describe their pain as of a "burning" character, and they insist that dry heat exaggerates it. Furthermore, they frequently seem most comfortable when the foot is almost or entirely uncovered and exposed to the air. In the acute exacerbations any covering that comes in contact with the affected part gives rise to excruciating agony.

Ulcerations, small or large, practically always give rise to exquisite pain and the toes affected—for the ulcers are practically always at or around the nails—assume a purplish-red, swollen appearance, at times looking as if they would burst open at any moment, and would take great joy in doing so. Conservatism—ultra-conservatism, is to be pursued in the presence of these affairs, for while ulcers they are, they are also gangrenous patches in reality, and it is best to let them alone, since they will heal only if the blood supply to the foot is improved. Wet boric compresses or salt solution may be used, occasionally boric ointment or plain vaseline, or anything bland and mild. The parts must be kept thoroughly clean at all hazards to avoid ascending infection, and as little sloughs appear they should be gently wiped away. If the ulceration progresses and involves the phalanges, adequate drainage should be provided, but a waiting course is always to be pursued.

Operative measures, even minor ones, only too often end in disaster, since with the terminal circulation already in a precarious state the resultant wound not only refuses to heal but often sloughs more than ever, with the result that more bone becomes involved, tendons become exposed and slough, and finally the process spreads up the foot. If then further operative measures are invoked the same story is repeated—it is usually one amputation after another until the whole leg is involved. Far better is it to be conservative. The patient may suffer a little longer, for in the vast majority of instances the ulcerated areas are exquisitely sensitive and each dressing is an agony; he may get extremely restless and the surgeon may at times be tempted almost beyond endurance to use the knife, but waiting is the only way I know

to achieve success. The cause of the trouble is not in the toes nor in the foot; it is in the occluded bloodvessels higher up, and one must bend his efforts to rectify this condition. As it tends to be corrected the pain becomes less excruciating, the edema of the foot and toes begins to subside, the color becomes more normal and healthy edges appear around the ulcers, which slough out and then heal, permitting the patient first to bear a little weight on the affected foot and then walk.

Should the measure as outlined fail, or should the pain become so unendurable as to preclude further conservative measures, one may resort to certain operative procedures. In a few instances it may be possible to do an arteriovenous anastomosis, by which means theoretically the blood current is shunted from the artery which is occluded below to the accompanying vein which is supposed to be patent throughout its extent. I have carried out a number of these operations and without mortality, but the procedure has gradually been discarded because experimentally at least it seems as if the blood current progresses down the vein but a short distance, after which it is turned back through venous lines of least resistance toward the heart. However this may be, certain of my patients appear to have benefited greatly by the operation, the gangrenous process was stopped and their pain relieved. It is only fair to say that the best results were achieved in young individuals who were suffering from Raynaud's disease. I do not believe an arteriovenous anastomosis is indicated in any of the more common forms of gangrene, since in most of those that have come under my observation the veins are involved in the process to a great extent, and in the very nature of things it would be impossible for the arterial blood to circulate through them. It may be that if one could get these cases in their earliest stages such an operation might be followed by good results, but I am of the opinion that equally good results could probably be obtained by other means if they were promptly instituted in the very earliest stage of gangrene. One must always remember that an artery which is occluded, say from the popliteal space down to the foot, is liable to undergo gradual occlusion all the way up to and into the pelvis, so that even if a successful arteriovenous anastomosis could be performed it would probably become occluded in the course of time by the ordinary progress of the disease.

But the success that follows the operation of arteriovenous anastomosis has been attributed to a cause quite distinct from that of the blood going down to the foot through the veins. It has been claimed by some that in the course of doing one of these operations the little nerve fibrils that are to be found in the sheaths of the vessels and in the walls themselves are cut, and that in



this way the relief of pain is obtained, so much so that recently Leriche has called attention to the great relief that has come about merely from stripping the sheaths from the affected vessels. It is still too early to say whether this is so, but his observation at least is interesting and will bear further watching.

In certain cases of threatened gangrene where amputation was not absolutely indicated, or where it seemed wise to procrastinate, I have ligated the femoral vein just below Poupart's ligament and above the entrance into it of the profunda vessels. The reason for this is that with all the channels of inflow to the affected member occluded, what little blood does get down to the foot is drained away too quickly by veins which are not occluded. In other words the patient's veins in these cases act as a suction apparatus, so that even where there is a fair amount of blood getting down to the distal parts of the extremity the tissues are not bathed in the necessary blood and blood juices long enough, because of the fact that the blood is literally sucked away too rapidly. That this is true one can tell by the fact that the venous pressure in these cases is practically *nil*. I have carried out this very mild operation of ligation in a number of instances, and have noted that the veins below, which were previously in a state of collapse, have at once filled out, the whole limb has taken on a bluish-red color, and from the very moment of ligation the temperature of the leg has risen. The venous pressure, too, which formerly had been negative, became positive and remained so. In addition to this, in several instances the pain has been definitely relieved and certain of the sloughing ulcers have taken on a healthy state and have gradually healed. None of my cases, however, have obtained permanent relief from this measure, so that I do not offer it as a cure. Perhaps if it were done in the early stages of the disease certain of the inevitable sequelæ might be avoided and a more lasting benefit might come from it. The procedure therefore is still in the state of trial.

The only operative measure, therefore, that remains is amputation, and in this connection a number of definite points must come in for consideration, far more, I think, than one would ordinarily believe. It is well known that patient's suffering from diabetes do not stand operation of any kind well, so that wherever possible they should not be subjected to such interference. This is especially true of those who have not only sugar in their urine but have acetone and diacetic acid as well. It is at times possible to free the urine of sugar but extremely difficult to get rid of the acetone and diacetic acid, and even when this is possible, general anesthetic and operation is extremely hazardous. In certain cases, though, the condition is such that the extremity must be removed and the patient take his chances. In others,

such as, for example, one that I now have under my care, it is possible to do an amputation by very slow, gradual and painless methods, at least an amputation that involves only about one-half of the foot. The man in question is quite weak, is on a most rigid diet and has acetone and diacetic acid, although he has been under a most rigorous treatment by a competent specialist for many weeks. It might be possible to take this patient's foot off, but the outcome is extremely doubtful, so that I am merely amputating one toe at a time as the gangrenous process permits. He is suffering from a slow, creeping form of gangrene, so that it is possible to remove the dead tissue without pain and therefore without anesthesia of any kind. In this way the patient's general condition is not all influenced. His hospital stay will, of course, be very much longer, but the outcome is far less problematical.<sup>1</sup>

In conditions other than diabetes the problem is not so difficult and depends mostly on the patient's age and general condition. A more pertinent question concerns the point at which amputation should be done. This remains an open one in the minds of most men, but as far as I am concerned my decision is made. In gangrenes consequent upon arteriosclerosis, thromboangiitis obliterans and allied conditions it is my custom to remove the leg just above the knee. I know full well that amputations below the knee are supposed to give better stumps for artificial leg purposes, but it has been my experience that in these conditions of gangrene, amputation performed below the knee only too often has to be followed by a secondary removal because of the fact that the stump does not heal. And this is not hard to understand, because of the fact that in nearly every case of this kind the artery is blocked almost throughout its entire extent, and since the leg is dependent on its collateral circulation for the most part it is only logical that there should be difficulty in healing. Indeed, this difficulty of healing is so great that even when amputation is carried out above the knee it is rare to get healing by anything like first intention, at least rare in my experience. In a certain few instances where the popliteal artery is still competent and pulsating it may be permissible to remove the leg below the knee; but even in these cases it is more than likely that in course of time this popliteal artery will become occluded and trouble will be encountered in the stump later as a consequence.

I have under my care at the present time a man, hardly thirty years of age, who is suffering from Raynaud's disease. He had one of his legs removed below the knee some eight to ten years ago. During all this time he has had to be on his guard con-

<sup>1</sup> Since writing the above a midcalf amputation was successfully accomplished on this patient.

stantly because of the development of little areas of necrosis in the stump. Indeed, it was months before the stump healed in the first place after the original amputation, and it was a year or more before he was ever able to wear a limb. At the present writing he is again in trouble with this stump and the question of higher amputation is under consideration. This man, by the way, came to me some four or five years ago when his right leg got into trouble. At that time his foot was gangrenous and I advised amputation above the knee. He refused absolutely to submit, so I was forced to do the amputation below the knee. The resultant stump never healed and the higher amputation was carried out some six or seven months later. There has been no trouble at all with this stump during all these years.

Within the last few months I have had another case sent me by a well-known surgeon who did his amputation below the knee. The patient was in the hospital seven months, and only then did the stump close by the removal of the projecting ends of both the tibia and the fibula. The resultant stump after this was so sensitive, the skin over it was so tense, and the tissues around the bones so atrophied that the patient never was able to use the artificial limb which he had procured. By appropriate massage, and by the use of the vibrator and constant prodding, I have succeeded in having this man use his artificial limb, but his complaints are continuous, and it is a foregone conclusion that eventually he will have to have another amputation above the knee. Experiences of this sort are not exceptional—they are the rule—so that my own mind is firm that amputation, in practically every case of the gangrenes I have mentioned, should be carried out just above the knee.

In the above pages I have attempted to describe the part played by pain in the various forms of gangrene. Insidious in its onset, extremely difficult to deal with, indescribably excruciating at times, it overshadows practically all other features connected with the disease. So much so that more than one limb that could have been saved has had to be sacrificed because the patient was unable to withstand the ravages of pain that went with his condition. But amputation is merely a conviction of weakness. Far better is it to save and to recreate rather than to destroy. I have pointed out various measures that in my hands have yielded results better than I had any reason to expect. It would be interesting to learn what results the same measures would yield in the hands of others.

## ORGANIZATION OF PNEUMONIC EXUDATES.

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THE purpose of this paper is (a) to show how the exudate in the lung alveoli starts to change into connective tissue, and (b) to throw light on the relation of organizing pneumonia to acute lobar pneumonia.

The organization into vascular fibrous tissue of intra-alveolar lung exudates, especially as this occurs in wide areas following an acute lobar pneumonia, has been extensively studied. Important contributions have been made by Laennec,<sup>1</sup> Marchand,<sup>17</sup> Cohn,<sup>31</sup> von Kahliden,<sup>32</sup> Herbig,<sup>33</sup> Ribbert,<sup>41</sup> Cornil,<sup>42</sup> Vogel,<sup>43</sup> Delafield,<sup>56</sup> Milne,<sup>74</sup> Kidd,<sup>75</sup> Kline<sup>79</sup> and others.

It has been determined that the intra-alveolar exudate of fibrin, including the exuded cells in its meshes, shrinks and condenses, thus leaving a space between it and the alveolar wall, though retaining contact with the wall by adhesions which may be either extensive or slender and filamentous. These connections between the retracted fibrin plugs and the wall may be formed of fibrin or of elongated cells. The fibrin, when originally deposited, is often continuous from space to space through the pores of Cohn,<sup>31</sup> which establish fine connections between adjacent air spaces belonging to different infundibula, and, when general retraction of the fibrin exudate occurs, these communicating strands stand out very distinctly. Pulmonary epithelium and other exuded cells appear in the gaps between the plugs and space walls, and some of the flattened epithelial cells, which have a spindle form when seen on edge, are often applied to the plug surface. About two weeks after the onset of the pneumonia, cells with elongated nuclei, exhibiting all transitions to fibroblasts, appear within the substance of the fibrin plugs and on their surface. At this time, or a little later, capillary vessels given off from the capillaries of the space walls enter the plugs by traversing the above-described adhesions between the space wall and plug. This process and also the communicating bands which traverse Cohn's pores, and later are changed into connective tissue, have been demonstrated beyond doubt by means of serial sections by MacCallum<sup>60</sup> and others. As time passes the fibrin is more or less completely absorbed and replaced by fibrillated connective tissue, and then the appearance of two networks is produced in sections, one the alveolar walls and the other the organized intercommunicating exudate. The alveolar walls also show varying degrees of fibrous thickening which may reach the point of obliterating the gaps between them and the fibrin plugs, so that the distinction between organized exudate and

basic lung structure, that is between the two networks, is completely lost and the whole tissue changed into a dense connective-tissue mass, devoid of spaces, tough and airless.

There has been much discussion about the origin of the connective tissue in the plugs, some observers thinking it an ingrowth either from the pleura and interlobular septa (Eppinger,<sup>11</sup> Cohn<sup>31</sup>), or from the bronchiole walls (Ribbert,<sup>41</sup> Herbig<sup>33</sup>), or from the walls of the air spaces (von Kahliden<sup>32</sup>). Others have thought that fibrogenic cells migrated into the plugs (Aufrecht,<sup>40</sup> Cornil<sup>42</sup>), or that a late secondary exudation of fibroblasts occurred not evoked by the original bacterial irritant (Ziegler,<sup>65</sup> Josephson<sup>24</sup>), or that cells originally exuded changed into fibroblasts (Marchand<sup>17</sup>). Still others have believed that the pulmonary epithelium surrounded and entered the plugs and became connective-tissue cells (Woronochin,<sup>8</sup> Linder-mann<sup>26</sup>), but this view has never been generally accepted. Perhaps the strongest current of recent opinion sets toward the derivation of the connective tissue, along with the vessels, from the wall of the air space in which each plug lies, though extensions of connective tissue into the plugs from pleura, interlobular septa and bronchiole walls, confirmed by various observers, are regarded as established but exceptional phenomena.

Organization of intra-alveolar exudates, as described, has been observed in bronchopneumonia, in tuberculous consolidation and about infarcts and abscesses (Frankel<sup>36</sup>), but its most extensive development, and that which has attracted the most attention, is as a sequel of lobar pneumonia. Here the lesion is seldom co-extensive with the original pneumonic exudate, but involves portions only of the lung originally inflamed.

The question whether the lobar pneumonias which go on to organization are a separate type of lesion from the outset or whether appropriate causes may effect this change in any lobar pneumonia is still undecided. Those who hold the latter view name as causes debility (Heschl,<sup>5</sup> Milne<sup>74</sup>), alcoholism (Marchand<sup>17</sup>), presence of excess of fibrin (von Kahliden<sup>32</sup>), excessive sluggishness of the lymph circulation (Köster<sup>19</sup>), insufficient pus cells in the exudate to effect its absorption (Flexner<sup>54</sup>), and the presence of an excess of serum (Kline<sup>79</sup>).

My contribution is based on the study of two sets of material—namely, (a) 603 lung sections, practically all showing pathologic changes of some kind, obtained from 249 cases whose autopsies I either did or attended. In many of these cases I studied the patients during life, and in all of them there are full clinical, autopsy and microscopic records; (b) 153 lung sections given me by Dr. Delafield, obtained by him at autopsy, all showing some lesion. In only a few of these, however, are clinical and pathologic records available.

Before analyzing the observations on this material it is neces-

sary to define what an intra-alveolar connective-tissue plug is and to discuss briefly some general characters of pneumonic exudates.

A typical connective-tissue plug of fairly recent origin, perhaps two or three weeks old, is composed of a dense, refractive substance taking a strong eosin stain. It is of a finely granular structure and may also show a distinct fibrin reticulum, either compact or, in places, more open (Fig. 1). The plug does not fill the alveolus in which it lies but regularly leaves a residual space which may be empty, or may



FIG. 1.—Organizing pneumonia, death on the twentieth day. Typical organizing fibrin plug adherent to the alveolar wall at A, but leaving a residual space elsewhere. Elongated fibroblast nuclei may be seen in the plug.  $\times 263$ .

contain polynuclear, mononuclear, blood or epithelial cells. Some flattened epithelial cells are often applied to the plug surface and have a spindle form when seen on edge. In sections a plug may appear to lie free in the alveolus, or it may be connected in part to the alveolar wall, either through broad areas of contact or by slender strands or bridges of fibrin or of cells. Tenuous strands may also extend through mural pores and so connect the plug to

plugs in neighboring spaces (Fig. 2). The dense plug substance often looks incompletely separated into rounded masses by partial fissures. In the plug are regularly included nuclei, some polynuclear and often pyknotic and deformed; others large, vesicular and rounded; and finally oval or distinctly elongated vesicular nuclei which can be seen in all stages of elongation until they appear as fibroblast nuclei with their cell bodies and associated fibrils sharply



FIG. 2.—Organizing pneumonia. Slender fibrin strand connecting adjacent plugs through a Cohn pore.  $\times 213$ .

distinct (Fig. 1). When simply oblong without defined cell body these early fibroblasts do not resemble the epithelial cells applied to the plug surface, but when the long cell bodies appear, and before the characteristic fibrillar ground substance is deposited, I know of no way of distinguishing the early fibroblasts which lie near and parallel to the surface, from the epithelial cells lying against the plug, as above described (Fig. 3). It is evident that in this difficulty lies the origin of the belief of some observers, above referred to, that epithelium may be metamorphosed into connective tissue. Fibroblasts deep in the plug substance, however, and

penetrating it in different directions, may, I believe, be safely identified as such.

I have gained the impression that pyknotic and deformed nuclei are more numerous in early plugs, twelve days or so old, than in late ones, three or four weeks old, and that some of the cells in the plugs, especially the polynuclears, are destroyed and disappear, while some of the mononuclears go on to develop into fibroblasts (Fig. 4).



FIG. 3.—Organizing pneumonia death on the twentieth day. Spindle-shaped cells along the plug edges, some separate and some adherent; impossible to say which are epithelium and which fibroblasts.  $\times 213$ .

Bloodvessels budding from mural capillaries unquestionably penetrate these plugs, but I am convinced that they do not penetrate them all or even a majority of them in the early stages, that is, not until after four or five weeks.

When occurring in any number, the dark red anastomosing plugs with elongated nuclei and fibroblasts are strikingly evident at the first low-power glance (Fig. 5), but in order to determine whether there is definite evidence that the exudate in a particular



alveolus promises to organize and so shall be considered an early connective-tissue plug, certain criteria must be set up. It is evident that the amount of retraction and of condensation of the fibrin is not a significant feature and will be the less developed the earlier the stage of the process. It is also evident that the same will be true of the ingrowing capillaries.



FIG. 4.—Pneumonia secondary to bronchoesophageal fistula. Fibrin plug with some elongated nuclei and many pyknotic polynuclear nuclei.  $\times 213$ .

Every alveolus which contains reticulated fibrin or a dense granular mass of exudate with a strong affinity for eosin and elongated vesicular nuclei in the fibrin mass, exclusive of those which may be confused with epithelium as above described, promises organization of its exudate, and has been considered to contain an early connective-tissue plug in the present study.

In order to justify this statement it is necessary to consider certain components of pneumonic exudates.

Fibrin varies greatly in quantity. Only rarely does it occupy as

much or more space than the cellular elements as a whole. It may be totally absent, so far as this can be established, through the absence of any demonstrable strands, fibrillæ or reticulum in the spaces. It not infrequently is very unevenly distributed, occurring in large and even overwhelming quantity in a few spaces and scarcely recognizable in most of the rest. Moreover, it is frequently asym-

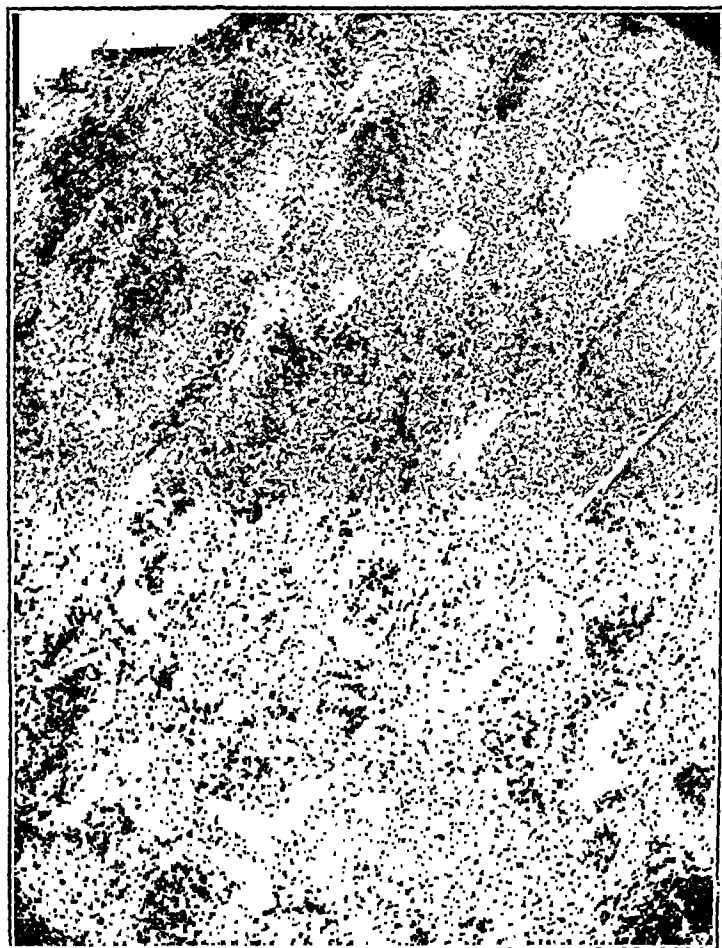


FIG. 5.—Organizing pneumonia, death on the twentieth day. Typical organizing intra-alveolar plugs with some thickening of the alveolar walls.  $\times 63$ .

metrically deposited in individual spaces, forming a dense reticulum on one side and fraying out to fine isolated fibrils in the opposite portion (Fig. 4). Such asymmetrical concentrations apparently often form the basis of connective-tissue plugs. In many sections I have observed such concentrations along the pleural boundaries, the fibrin being regularly denser on the side next the supporting tissue (Fig. 6). The same observation has been made by Cornil.<sup>42</sup> I can suggest no reason unless these portions of the alveoli move less with respiration, and so the fibrin is less stretched and less insufflated by the tidal air during its deposition. The subsequent

formation of plugs in such regions, to the exclusion of others, perhaps explains the view advanced by some observers that the connective tissue of the plugs is derived from pleural and trabecular connective tissue. At any rate the fibrin is usually unequally distributed, a lot in some spaces, very little in others and often asymmetrically deposited in individual spaces, so that a partial absorption of the exudate would result in leaving fibrin plugs only partly filling the spaces, a probable factor in plug-production as



FIG. 6.—Lobar pneumonia, death on the eighth day. Fibrin concentrated in alveoli along a large vessel and mostly on the side of the spaces next the vessel sheath.  $\times 40$ .

well as subsequent shrinkage and condensation. It is not at all unusual to see sections, especially of pneumonias dying within two weeks of their onset, with a large number of typical dense red staining fibrin plugs which show no elongated nuclei (Fig. 7). Whether these represent the earliest stage of connective-tissue plug formation, and whether fibroblasts would subsequently have appeared in them had life been prolonged, as Delafield<sup>66</sup> thought, I have no way of knowing. At any rate they are excluded by the above definition from the plugs with indications of organization. There is no obvious reason why they cannot be absorbed as well as any other fibrin exudate.

Serum is coagulated in various forms by hardening agents and appears in lung sections as fine granular matter, as a foam work or as a homogeneous coagulum enclosing cells and some round lacunæ, presumably air bubbles. When in the latter form it may stain very faintly or very strongly with eosin, apparently depending on how much blood pigment it held in solution when coagulated. Kline,<sup>79</sup> as a result of experiments on dogs, inclines to the belief that serum is an essential factor in the production of organizing



FIG. 7.—Lobar pneumonia. Fibrin plug without fibroblast nuclei.  $\times 213$ .

pneumonia; but I have never seen long vesicular nuclei or fibroblasts in even the deepest staining serum coagula in lobar pneumonia, and almost never in sections of other lesions. One most striking alveolus from an organizing pneumonia contained a homogeneous serum coagulum, in the central part of which was included a distinct wisp of fibrin fibrillæ. In the serum were several cells with round vesicular nuclei but none elongated, while those in the fibrin were definitely elongated and of the early fibroblast type

(Fig. 8). I can see no reason for believing that exuded serum favors the development of fibroblasts as exuded fibrin does.

The relations of the exuded cells to the connective-tissue plugs are various. Red blood cells are often included in the plugs, but in no section did fibroblasts appear in alveoli filled with blood alone even when it had probably been there for some time.

Polynuclears are, of course, entangled in the reticular fibrin or included in the dense plugs, often in large numbers; but they seem



FIG. 8.—Organizing pneumonia, death on the thirteenth day. Large alveolus filled with coagulated serum, with a mass of fibrin in the center. The nuclei in the serum are round, some of those in the fibrin are distinctly elongated.  $\times 213$ .

to exert no influence on organization. In fact, as above mentioned, they undergo degeneration with pyknosis of their nuclei (Fig. 4), mostly before the end of the second week from the onset in lobar pneumonia, so that after that time few are seen in the plugs.

The epithelium is often seen applied to the plug surface, as above mentioned (Fig. 3), whether as a result of simple desquamation from the space wall or by a true investing proliferation, as has been thought by some observers, it is difficult to be sure. The difficulty

of distinguishing such cells from fibroblasts has already been explained. Sometimes definite dense retracted plugs with typical long vesicular nuclei occur where no reticulated fibrin can be demonstrated in any of the alveoli in the section, but where there is much desquamated epithelium, and all stages can be traced from loose, discrete, desquamated epithelial cells in some alveoli to their conglomeration into dense plugs in others, in some of which elongated nuclei occur (Fig. 9). Thus the formation of

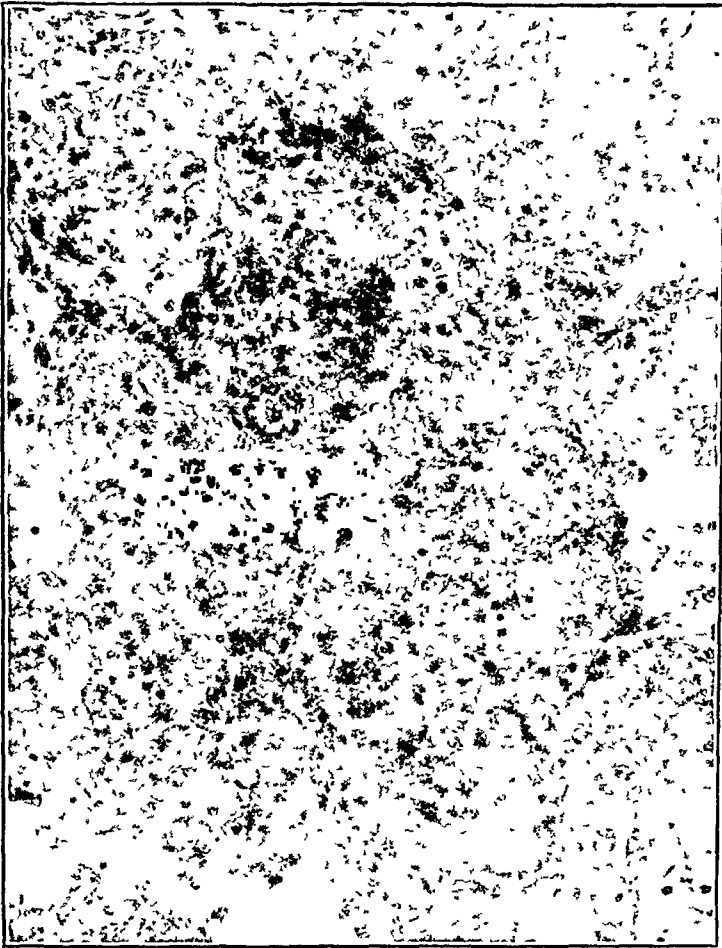


FIG. 9.—Secondary bronchopneumonia in an adult. Much epithelium in the alveoli, in one case concentrating to form a plug. Fully formed plugs with elongated nuclei and traces of their epithelial composition still distinguishable occur in the same section.  $\times 213$ .

organizing plugs out of epithelium instead of fibrin apparently occurs, though rarely. Of course, some fibrin-binding substance may be present in such cases without presenting the usual reticulated appearance.

As already stated the fibroblasts are derived from cells with a single rather large vesicular nucleus. Much has been written

about such cells in inflammatory processes, and I have no new light to throw on their origin. They presumably belong to the mesenchyme group, and I believe they exist in the intra-alveolar exudate from the start rather than that they represent a secondary migration induced by a new stimulus, because they lie deep in the dense fibrin plugs when they first take on the oblong shape. Mononuclear cells occur in most intra-alveolar exudates—some have no visible cell body and a small dense nucleus, the lymphocyte or round-cell type; some have a larger vesicular nucleus and an appreciable cell body, the endothelial type, and may be hard to distinguish from pulmonary epithelium. How many kinds of cells the mononuclears represent, from how many sources of origin, whether they arrive through the blood or lymph channels, what their various functions and destinies may be, is still somewhat uncertain. That one group of them may become fibroblasts, however, is generally accepted. The only new ideas I have to offer about them in organizing pneumonias is that they exist in the exudate from the start (a suggestion made long ago by Marchand<sup>17</sup>), that the presence of fibrin in some way favors their change into fibroblasts and that this change is not dependent on the ingrowth of buds from mural capillaries because fibroblasts regularly begin to develop before any vessels appear and may often attain full development where no vessels can be demonstrated. If the fibroblasts were derived from the mural connective tissue by ingrowth, as the vessels are from the mural capillaries, it should be easy in early stages to see spots in the plugs from which the connective tissue radiated, an appearance I have not seen, instead of a simultaneous change in shape of nuclei scattered all through the plug, which is the usual appearance.

Just as fibrin plugs may be present in many spaces without the presence of any elongated vesicular nuclei, so cells with such nuclei and even definite fibroblasts may occur in the alveoli, without any fibrin and without any plug formation; but I have not met this condition in lobar pneumonia or secondary patchy pneumonia, though in tuberculous lungs it is not very rare (Fig. 10).

The new bloodvessels, about which so much has been written and the manner of whose ingrowth has been demonstrated beyond question in serial sections by MacCallum<sup>50</sup> and others, have not proved as universal as I expected. In fact, not only have they been absent from entire sections showing early plugs with definite early fibroblasts, but quite difficult to find in some lesions of long standing, notably in a case of four and a half months' duration.

Conservatism must be exercised in interpreting vessels as newly formed and pathologic, for the vessels in the normal partitions which partially separate the alveoli springing from the same infundibulum often appear to penetrate or jut into the plugs just as they do in any exudate that occupies the alveoli (Fig. 5).

On the other hand, small thin-walled single vessels cut in cross-section, or short and isolated oblique slices lying in the central portion of the plugs, are definitely newly formed and inflammatory (Fig. 11). This opinion that new-formed vessels in the plugs are not essential and, in many cases, not even a frequent feature of the lesion under discussion, is based not only on the study of ordinary hematoxylin-eosin preparations but also from the careful examination of a number of sections of organizing pneumonias



FIG. 10.—Subacute phthisis. Fibroblasts growing in an alveolus with no fibrin and no condensation of the cellular exudate into a plug.  $\times 213$ .

among the slides received from Dr. Delafield, in which he injected the pulmonary vessels with a gelatin Prussian-blue mass, in which the capillary ramifications may be accurately traced.

Connective-tissue plugs, as above defined, are by no means rare in the material studied. They appear in 129 out of my 603 sections and in 48 out of the 153 made by Dr. Delafield, that is, in 23.4 per cent, or over one-fifth of all sections examined.

The term organizing pneumonia has been applied to cases in which



the organizing intra-alveolar plugs are numerous, the lesion of lobar distribution and not tuberculous in origin, especially if the patient first falls sick as a lobar pneumonia. Nine of my cases fall in this group, and it is from them that the sections diagnosed as organizing pneumonia were taken. A study of the records of these cases does not support the view of some observers that old age and debility are important etiologic factors. Thus the average age is forty years, the youngest twenty, the oldest seventy-two, and

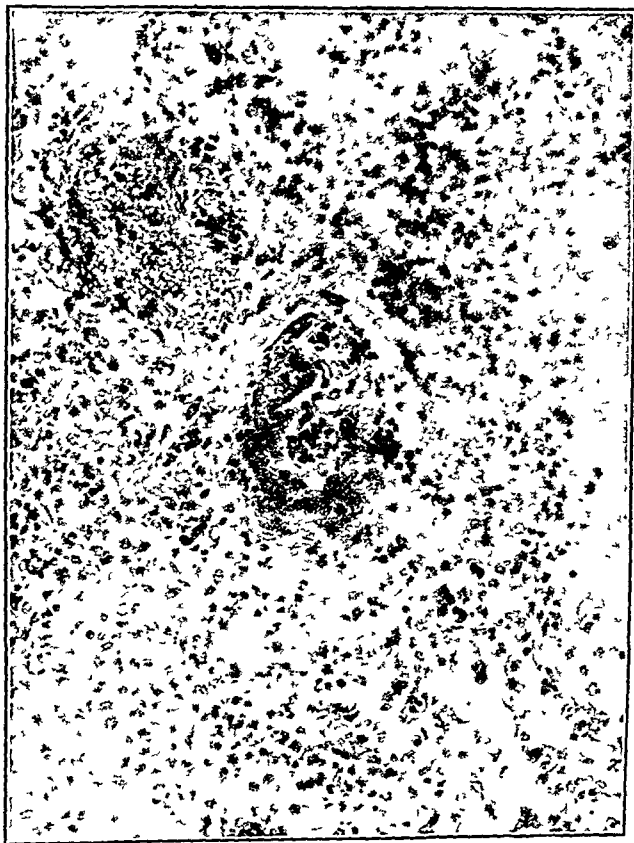


FIG. 11.—Pneumonia secondary to bronchoesophageal fistula. New-formed vessels in an organizing fibrin plug.  $\times 213$ .

only 1, the last mentioned, over sixty. The nutrition and previous general health, as far as it can be determined from the records, was fair or good in all but 2. Excessive use of alcohol is only reported in 1 case. Seven out of 9 of my series were males. The onset was sudden and identical with that of ordinary lobar pneumonia in 6, but of a more gradual character in 3, the most indefinite being in the old man of seventy-four years, who was, however, feeble-minded and unable to give a reliable account of himself, and of

the other 2, one in a man, very sick, who was taken ill three months before admission, where recollection of the type of onset could well have been confused.

There is nothing significant about the location of the consolidation, as is evident from the following table:

Entire right lung, 3.

Entire left lung, 2.

Entire left and part of right lung, 1.

Right upper and middle lobes, 1.

Both lower lobe, 1.

Right upper lobe, 1.

Left lower lobe, 1.

In 6 cases there were fibrous pleural adhesions; in 2 cases a fibrin exudate. The duration varied from eight to one hundred and thirty-five days. The average from 8 cases being forty days. Other lesions of lung and pleura were frequently present. Abscesses or cavities or both occurring in 5 cases and a double empyema in a sixth one. The microörganism was only determined in 2 cases: 1 a pneumococcus type I and the other a pneumococcus type II.

The intra-alveolar plugs themselves present different stages in the process already described in detail. As has been above indicated new vessels in them are not frequent, being notably hard to find in the case of a hundred and thirty-five days' duration, and only found in 3 others of the series, 1 of uncertain duration and the other 2 of thirteen and thirty-five days respectively.

This series of 9 organizing pneumonias is very similar in general to other series that have been reported, though the case of eight days' duration is a very early one. Cavities, abscesses and pleural adhesions have been many times observed as concomitant lesions. I have given this recapitulation of my cases not to illustrate any new features, but rather to show that my observations are based on true cases of organizing pneumonia similar to those reported by other observers.

It is evident not only from my small series but from the literature that organizing lobar pneumonia is not a rare lesion at autopsy. On the other hand a healed lesion corresponding to it, that is a lobe extensively changed into connective tissue, is a decided rarity. Such cases when found may be impossible to distinguish from cases which have started as bronchopneumonias or from cases primarily pleurogenic. I have seen but one such case in an adult with extensive fibrosis of the lung tissue and multiple large bronchiectasiæ involving the right upper and middle and the left lower lobes in a woman, aged forty-eight years, without any history of previous lung trouble.

The deduction from all this is that organizing lobar pneumonia, once fully established, proves fatal in the vast majority of cases.

Organization of the intra-alveolar exudate, however, is not at

all confined to sections from cases in which the lesion is pronounced enough to be called organizing pneumonia, as shown by the following list of the anatomic diagnoses of the sections in my own series which show organizing plugs:

Organizing pneumonia . . . . .	31
Lobar pneumonia . . . . .	38
Bronchopneumonia . . . . .	5
Secondary or patchy pneumonia . . . . .	5
Tuberculosis pneumonia (all forms) . . . . .	27
Interstitial pneumonia . . . . .	6
Infarcts . . . . .	5
Lymphatic leukemia . . . . .	3
Congestion and edema . . . . .	3
Pneumonia secondary to bronchoesophageal fistula . . . . .	1
Chronic congestion with heart disease . . . . .	1
Cancer . . . . .	2
Compressed lung beneath empyema . . . . .	1

The incidence of organizing plugs in the ordinary forms of consolidation is shown in the following table, again from my own series:

	Total number of sections exhibiting this lesion.	Number of sections of this lesion which show organizing plugs	Sections of this lesion showing organizing plugs. Per cent.
Lobar pneumonia . . . . .	101	38	37.6
Bronchopneumonia . . . . .	55	5	9.9
Secondary or patchy pneumonia . . . . .	59	5	8.4
Tuberculous pneumonia (all forms) . . . . .	87	27	31.3

Organizing plugs are most frequent in lobar pneumonia, and here also the fibrin plugs without early fibroblasts are most often seen. Of 16 sections in which fibrin plugs without fibroblasts occur, 9 are in sections of lobar pneumonia. In lobar pneumonia dense fibrin, one of the components of organizing plugs, is present in some alveoli in nearly half the sections, and in many such specimens some elongated cells appear in the fibrin. There is thus more or less incipient organization of the exudate in over one-third of all lobar specimens examined, but the lesion does not reach sufficient development or extent to warrant calling it organizing pneumonia. In other words the sections of lobar pneumonia and of organizing pneumonia, taken together, apparently represent a series exhibiting various degrees of organization from none up to the extensive examples, and the line of definition between lobar pneumonia and organizing pneumonia becomes an arbitrary one. Numerically stated, of 134 sections of lobar consolidation 54 show no tendency to organization, though fibrin and mononuclear cells regularly occur in the exudate; 9 show distinct dense fibrin plugs but no elongated nuclei; 38 show organizing plugs but not in sufficient numbers to be called organizing pneumonia; while 33 must be considered frank organizing pneumonia.

The proportionate figures hold also in general for the cases

from which these sections were taken: of 48 cases of lobar pneumonia, 24 showing no organization, 15 showing minor amounts of organization and 9 being classed as organizing pneumonia.

On this basis I believe that organizing pneumonia, or the "lobar pneumonia with connective tissue" of Delafield, is not a separate lesion or disease but rather a variety of lobar pneumonia, the extreme expression of a tendency that exists in many cases of lobar pneumonia.



FIG. 12.—Persistent bronchopneumonia in an adult. Many organizing plugs in alveoli near an inflamed bronchus.  $\times 35$ .

In bronchopneumonia organization of the exudate in the bronchial wall is, of course, very frequent, but the formation of the connective-tissue plugs here under discussion is comparatively uncommon—5 times in 55 sections in my series. Age may be a factor, though typical plugs are present in sections from an infant under one year. In the Delafield sections there are several from persistent bronchopneumonias in adults in which organizing fibrin plugs form a prominent feature of the lesion (Fig. 12).

In the secondary patchy consolidations which occur as terminal lesions in many conditions, especially in adults, intra-alveolar organization is again comparatively uncommon, 5 sections out of 59 in my series. In these cases there is in general more serum and red cells and less fibrin, but how much this composition of the exudate has to do with a relatively smaller number of plugs, I do not know.



FIG. 13.—Tuberculous pneumonia. Organizing plugs in many spaces.  $\times 35$ .

In tuberculous inflammations of the lung, on the other hand, a large proportion of the specimens, 27 out of 87, show organizing fibrin plugs, and in some cases of phthisis the lesion seems to be based on the development of connective-tissue plugs in nearly every alveolus, necrosis of this exudate subsequently occurring over areas of varying extent (Fig. 13). Here mononuclear cells are often predominant in the exudate, and instances in which they are changing into fibroblasts in spaces in which no fibrin and no plug substance are present are not very unusual. In lobar pneumonia the dense fibrin plugs are common and the fibroblasts com-

paratively rare; in tuberculous pneumonia, on the contrary, I have found the fibroblasts numerous, even developing when there is no fibrin, and when fibrin is exuded, fibroblast nuclei readily develop in it.

Organization of the pneumonic exudate has generally been regarded as beginning about the fourteenth day after the onset of the symptoms, perhaps because it was thought that the new con-

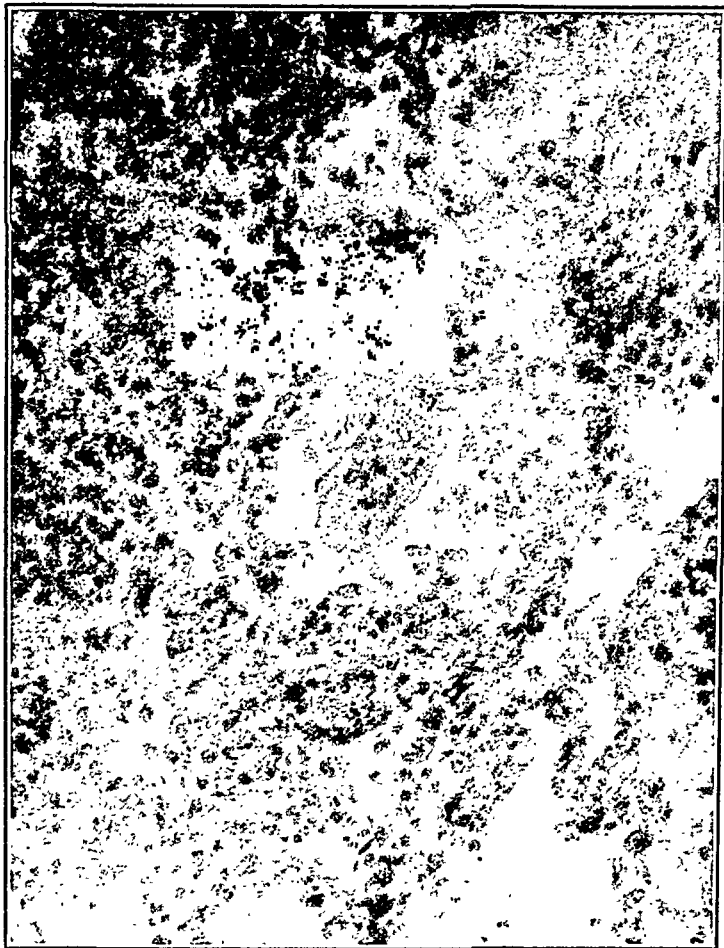


FIG. 14.—Lobar pneumonia, death on the fifth day. Fibrin plug with elongated nuclei.  $\times 263$ .

nective tissue was derived from the alveolar wall along with the budding capillaries which are first demonstrable at about this date. Cornil,<sup>42</sup> however, describes elongated fibrogenic nuclei on the seventh day in human pneumonia, and on the sixth day in experimental pneumonia in dogs. My belief that the fibroblasts develop from cells contained in the original exudate, especially in the presence of fibrin, but antecedent to and quite independent of the vascularization of the plugs, is confirmed by finding elongated vesicular nuclei in fibrin plugs in 2 cases of lobar pneumonia dying

on the fifth day (Fig. 14) and in 2 other cases dying on the sixth day, and also 1 case, classed as organizing pneumonia, dying on the eighth day.

There is an obvious objection to the ideas here presented, namely, the fact that, clinically, cases of organizing pneumonia are decidedly unusual while complete resolution occurs in the vast majority of the lobar pneumonias that recover. Moreover, in those of my cases which died, where the duration of the disease was known, the average day of death in those with no organization or with plugs in which the nuclei are not typically elongated, was the eighth day, while in those with organizing plugs it was the ninth day—not a significant difference. There is no evidence, however, and no reason to suppose that the presence of oblong or oval nuclei in a plug of intra-alveolar fibrin interferes in any way with its complete solution, or that the condition which exists in a lobar pneumonia when it contains many such plugs is any more resistant to resolution up until about the fourteenth day than the cases with no indications of organization. After the cells have fairly become fibroblasts, on the other hand, and especially after the deposition of fibrillar ground substance, usually somewhere between the fourteenth day and the twenty-first day, resolution must become progressively more difficult in that part of the consolidation where such organization is proceeding.

Another objection to the theory here presented is that organization of a few intra-alveolar plugs would seem not unlikely in many cases of lobar pneumonia, for there are numerous cases in which some signs and some roentgen-ray shadows persist after three weeks, to clear up gradually but completely later on, and in such lungs there ought to be left some traces of the process. It is, however, well established, on the other hand, that resolution may be delayed and sluggish without any organization of the exudate or without its development to the true fibroblast stage, and, on the other hand, a few scattered alveoli changed into connective tissue would be hard to find and practically impossible to identify years later when they would simulate an interlobular septum or vascular sheath.

On many points I can offer no light: Why incipient organization is regularly snuffed out by resolution, but sometimes goes on to the full development of a permanent fatal lesion? What makes the exudate contract into plugs? Why fibrin favors the growth of fibroblasts? What are the origin, function and destiny of the various mononuclear cells in pneumonic exudates? How the fibrogenic cells may be identified? and many others.

I believe, then, that pneumonic exudates organize by the metamorphosis into fibroblasts of cells originally exuded and that this change is favored by the presence of fibrin. I further believe that organizing pneumonia is the extreme development of a process which begins in a great many lobar pneumonias and is thus a sequel or complication of lobar pneumonia rather than a separate pathologic process.

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## OBSERVATIONS ON THE CURABILITY OF GASTRIC ULCER, WITH A REPORT OF FOURTEEN CASES OF HEALED LESSER CURVATURE ULCERS.<sup>1</sup>

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GASTRIC ulcer of the lesser curvature type when subjected to medical treatment affords a good opportunity for observation during the period of healing and thereafter. Medical literature is as yet meager as to the number of such observations and the possibilities of medical cures. I deem it therefore worth while to report a series of 14 cases of gastric ulcer of the lesser curvature type presenting a niche anywhere between the two incisuras, either overriding the lesser curvature or close to it. All these have been subjected to medical treatment and have been observed for periods ranging anywhere up to four and a half years. Up to the present time all these ulcers have remained healed. This statement is based not only upon the subjective clinical evidence of the improvement and well-being of these patients, but upon definite objective data as recorded from time to time on roentgen plates, where not only a disappearance of the ulcer crater is noted, but also a restoration of

<sup>1</sup> Read before the New York Physicians' Association, May, 1921.

the stomach wall to normal outline as well as the passing over of peristaltic waves.

I present these cases not with the attempt to compare the respective value of medical and surgical therapy, nor with the attempt to exploit one method as being more meritorious in its results, for each, as we shall see, has its definite indications. I wish, however, to indicate the type of gastric ulcer which is most amenable to medical treatment and to show the changes that occur in the morphological appearance of the lesion as well as the alterations in the physiological function in the stomach as manifested by the character of the tone, peristalsis, spasticity, motility and secretions. These studies were made chiefly by the aid of the roentgen-rays and also by ascertaining from time to time the chemistry of the gastric secretions. All these were conducted coincident with careful observation of the clinical picture in each case.

It would not be amiss to mention briefly at this point the distinguishing characteristic features of this type of ulcer as compared with ulcers situated in other parts of the stomach. All peptic ulcers, by virtue of their different anatomic locations, produce profound and diversified alterations in the normal physiological gastric function, and are accompanied by a varied train of symptoms. Each forms a definite clinical entity that can be differentiated and recognized.

**Gastric Ulcers.** Those situated in the midgastric region between the incisura cardiaca and the incisura angularis and giving rise to the craters, the so-called "Haudeck niche." They most often override the lesser curvature, when they are spoken of as saddle ulcers, but they may also appear on the posterior wall close to the lesser curvature, but seldom on the anterior wall. They are subdivided according to depth, and comprise the mucous, the penetrating and the chronic perforating ulcers. They are characterized by spastic manifestations of the greater curvature opposite the level of the ulcer, but most often the entire stomach manifests a diffuse gastrospasm, causing the antral and pyloric portions to assume a corkscrew or spigot-shape. Disturbances in the motility are not common. When present they are due to the associated reflex pylorospasm. They usually occur at a later age in life than the pyloric or duodenal ulcers. Vomiting is often present. The pain comes on earlier and is always referred to the left side of the abdomen and backward toward the left side of the spine. Tenderness invariably is present and may at times be manifested by marked rigidity, depending upon the acuteness of the stage and the associated perigastritis. The tenderness corresponds to the location of the niche. The stomach appears extremely subtonic in type with a stretched-out, collapsed vertical portion and a broadened low-lying flaccid horizontal portion.

**Pyloric Ulcers.** Those situated close to or at the pyloric orifice give rise to interferences in gastric motility depending upon the various grades of induration, cicatrization and stenosis of the pyloric orifice. The stomach in time becomes atonic, is very large in size and eventually results in gastrectesia. In addition to pain, vomiting is here a prominent symptom, the vomitus containing food particles partaken twenty-four hours or more before. The pain is usually situated to the right of the median line and may be referred to the right nipple or to the back.

**Duodenal Ulcers or Post-pyloric Ulcers.** Those situated beyond the pyloric vein are usually in the first portion of the duodenum. These comprise the majority of all ulcers, totalling about 78 per cent. They are divided into two classes, the compensated and the decompensated types. The first is characterized by an increase in tone, increased peristalsis, rapid motility and late hyperacidity and hypersecretion. Such stomachs usually empty within two or two and a half hours. The pain develops usually after the food has mostly passed out of the stomach and is caused by intense pylorospasm due to late hyperacid secretions.

The decompensated type of duodenal ulcer tends to approach more the condition encountered in the pre-pyloric ulcer, and as time progresses the differences between the two become indistinguishable. The pains are likewise referred to the right of the median line. Vomiting is seldom present unless encroachment upon the pylorus takes place with a resultant stenosis.

**Cardiac Ulcers.** These ulcers are rare. They give rise to painful deglutition and cardiospasm.

**Marginal and Jejunal Ulcers.** These form a class by themselves and comprise the so-called postoperative peptic ulcers.

In 1916 Hamburger<sup>2</sup> reported 2 cases of indurated gastric ulcer in which intensive medical treatment had been able to cause a disappearance of the niche and a return of the stomach to its normal outline and function in 1 case and a lessening of the size of the niche in the other. In 1910<sup>3</sup> he recorded an additional case in which after two weeks' treatment there occurred marked diminution in depth and width of the lesser curvature pocket, and after three months a complete disappearance took place. Seymour Basch also reported in December, 1920, before a local medical society, 3 cases with similar findings.

Ohnell,<sup>4</sup> in 1920, reported 34 similar types of ulcers treated medically between 1916 and 1918. Out of these, 31, or 91 per cent, revealed a complete disappearance of the niche. In 3 cases there was a diminution in size. Besides these, 8 other cases were observed

<sup>2</sup> Roentgen Studies in the Healing of Gastric and Duodenal Ulcers, Chicago Med. Clinics, November, 1916.

<sup>3</sup> Hamburger, W. W.: AM. JOUR. MED. SC., February, 1918, p. 204.

<sup>4</sup> Arch. f. verdauungskrankheiten, 1920, 27, H. I., p. 72.

in the clinic, likewise followed by a diminution in the size of the niche. With the exception of 1 case all of his patients became symptom-free, the tenderness over the niche disappeared in all, and wherever there was disturbed motility it became considerably improved. He concluded, however, that the period of observation was still too early to judge the final result of a permanent cure.

Buckstein,<sup>5</sup> in January, 1921, reported in detail 1 case in which careful medical treatment had caused a large niche to totally disappear.

All these studies, however, were conducted either during treatment or shortly after. My own experience dates back to October, 1916, when, during the same month, there came under my observation 2 cases of fairly large penetrating ulcers on the lesser curvature. In 1 case I had advised surgical intervention in view of the length of duration of the disease, the large size of the niche and the considerable disturbance in the motility of the stomach. There was intense spasm of the pylorus and a large ten-hour food rest. The pylorus appeared corkscrew-shape, suggesting almost the presence of malignancy. Considerable nutritional disturbances were also manifest. Operation was refused. The patient was therefore placed under medical treatment and closely observed. To my great surprise he greatly improved, the symptoms gradually disappeared and there was a noted gain in weight.

The second case, with a shorter history of illness and with less marked disturbances in motility, was likewise placed under medical treatment. About six months later, stimulated by the apparent well-being of both of these cases, my curiosity was aroused as to the morphological appearance of the lesion as well as to what changes in function might have occurred. I therefore submitted both of these cases again to a careful roentgenological examination. The niche on the lesser curvature had entirely disappeared and there was considerable improvement in gastric function. Shortly after these observations I communicated these findings to several colleagues, including Dr. I. W. Held, who later quoted this personal communication in his article, "Indications for Surgical Interferences in Ulcus Ventriculi."<sup>6</sup> Since then I have seen 12 more cases in which I have had the occasion repeatedly to observe and check up the roentgenological findings from time to time as well as the gastric chemistry. These cases have shown not only the roentgenological disappearance of the niche, but, with one exception, have been free from all gastric symptoms for periods up to four and a half years.

The type of treatment employed was not unusual or extraordinary. In none of these was duodenal feeding instituted. In only 3

<sup>5</sup> Roentgenographic Evidence of Ulcer Healing, Jour. Am. Med. Assn., January 22, 1921, p. 231.

<sup>6</sup> Held, I. W.: Indications for Surgical Interferences in Ulcus Ventriculi, Surg., Gynec. and Obst., December, 1918.

cases was oral alimentation totally withdrawn for two days. All were placed on a modified Lenhartz diet and were kept in bed for periods varying from two to four weeks, after which time a prolonged abstinence from extractives, red meats, pastries and spices was strongly insisted upon. Mental and physical rest was strongly urged after the period of active treatment. Medicinally, alkalies and belladonna in frequently repeated doses were administered. Liberal doses of mineral oil were also used. The effect obtained was not as prompt or as spectacular as in duodenal ulcers. The pain disappeared rather slowly and gradually, until at the end of two weeks there was a decided abatement in the symptoms. The disappearance of the niche can be followed from week to week and from month to month. It usually takes from six to eight weeks for a niche to completely disappear under medical treatment. Its gradual diminution in depth and width is accompanied by a coincident improvement in the clinical picture. The pains and distress disappear, vomiting ceases and the tenderness disappears as well as the boring pain in the back. Appetite returns to normal. There is a gain in weight. Hemoglobin improves. Gastric motility slowly returns to normal. In those cases in which complete mental relaxation and physical rest were carried out longest the symptoms disappeared completely and have since never returned; while in the others, all women in whom the constant nervous tension over the necessity of early resumption of their household duties was a prominent factor, the symptoms abated slowly and persisted for a longer time. After several months, however, they completely disappeared. One woman with a complicated cardiac disease, who had been rather indiscreet in her dietary restrictions, had two mild attacks of gastric distress during a period of eighteen months. Roentgen examination at each time has failed to reveal any recurrence of the lesser curvature pocket, nor was there any alterations in her gastric secretions. Slight regulations in her diet and rest, which was insisted upon more for her cardiac condition, promptly resulted in a disappearance of her symptoms. The secretions had undergone profound alterations.

Case 1, in which the greatest disturbance of motility was present, accompanied by a hyperacidity of 50 free HCl and 80 total acid and marked hypersecretions, developed in four and a half years a complete anacidity and an associated rapid gastric emptying. The majority continued to manifest hypersecretion, but the acidity curves became low.

Roentgenologically one could observe not only a disappearance of the niche, but the lesser curvature had returned to a normal outline, became smooth and later on peristaltic waves were seen to pass over the ulcer area. Hamburger remarks that its disappearance does not mean a complete normal restitution of the stomach wall, but probably is to be interpreted as simply the following of the

ulcer crater with organized tissue, and possibly the transformation of a penetrating ulcer into an indurated ulcer giving rise, as mentioned by L. G. Cole, to an "indurated area." He further states that the absence of the normal peristalsis is conclusive evidence that complete restitution with absorption of all connective tissue has not occurred.

The observations of Cole and Hamburger are correct. They however have made these observations during the period of healing or within a few months after. My own observations, which were carried out several years after the initial cure, have revealed a total disappearance of this indurated area and a complete restoration of the peristaltic wave. Only in one case, when treatment was poorly carried out, is there evidence after two years of an indurated area, and in another one there is a suspicion of a beginning hour-glass contraction.

The following is a detailed report of the individual cases. Out of 14 cases 11 were males and 3 females. Their respective ages ranged from thirty-three to sixty-five years, being greatest in this series between the fourth and fifth decades.

CASE I (Figs. 1 and 2).—S. F., male, aged fifty-six years, store-keeper, came under my observation in 1916. About eight years ago he had an acute attack of suppurative appendicitis. He was operated upon and made a good recovery. Felt well until about six years ago, when he noticed fulness and pressure in the epigastrium after meals. Later he developed a pain, cramplike in character, which came on about two or three hours after each meal, requiring him to rest in a supported stooping posture for about one hour, after which the pain would disappear. He had nausea, pyrosis, was afraid to eat and lost about fifteen pounds.

Physical examination revealed a man of moderate stature, thin, weighed 125 pounds, sallow complexion, pinched facies with an expression of pain, heavily coated tongue and cold, moist extremities. Reflexes normal. Pulse showed a moderate bradycardia. Cardiac sounds normal. Abdominal examination revealed at once a diffuse tenderness over the entire epigastrium, with a point of tenderness one inch above the umbilicus slightly to the left of the median line. There was some rigidity present suggesting a localized inflammatory condition, perigastric in origin. Abdomen otherwise not distended. No tenderness in the right iliac fossa.

A roentgenological examination revealed the stomach to be more of the atonic type, large, distended, with a large "magenblase" pushing up the left diaphragm higher than the right. There was a large penetrating ulcer of the lesser curvature about the size of a 25-cent piece. The pylorus showed evidences of intense spasm. It assumed a corkscrew-shape, suggesting malignant infiltration. The food passed out in a narrow stream. A ten-hour examination showed

a large crescentic residue with hypersecretion. This retention persisted for many hours after. There was a moderate amount of hyperacidity: 50 free HCl and 70 total acid. Operation was suggested in view of the large disturbance in motility, the large residue, the associated nutritional disturbances, and above all in view of the possible malignant changes. The patient refused operative interference. He was therefore put to bed and medical treatment instituted. It was surprising to see this patient begin to improve, his symptoms slowly disappearing. He gradually



FIG. 1 — Case I.

returned to a more liberal diet, gained in weight back to his normal condition and did not consult physicians any longer. About six months later he was sent for in order to check up the condition of his ulcer as well as to ascertain the functional capacity of the stomach. The large penetrating ulcer on the lesser curvature was entirely gone, leaving a perfectly smooth lesser curvature. The pylorus showed less irregularities, but the six-hour retention was still persistent, being, however, much reduced.

An examination on January 30, 1921, revealed the stomach to

have returned to a normal size and normal tone. The peristalsis was active and passed over uninterrupted on the lesser curvature. The emptying time was reduced to four and a half hours, while previously a ten-hour examination revealed a retention of over half the meal. The secretions changed from a hyperacidity to an anacidity. The patient continues to feel well and is free from all gastric symptoms.

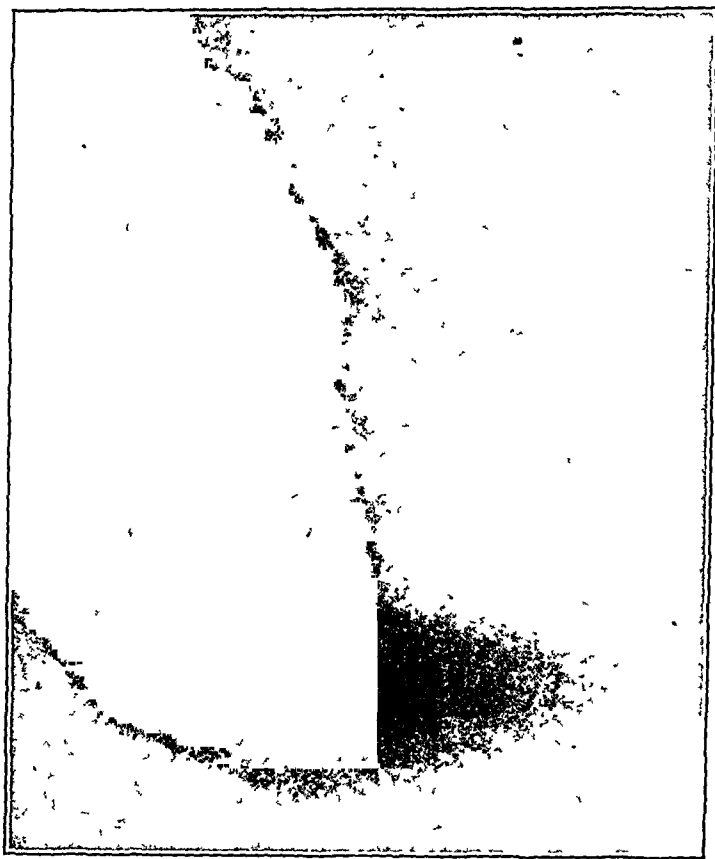


FIG. 2.—Case I.

CASE II (Figs. 3 and 4).—A. M., male, aged fifty-one years, trunkmaker, married, was referred by Dr. D. Barasch in October, 1916. Family history negative; habits moderate; does not use liquors; smokes moderately; denies venereal diseases. Present history dates back five and a half years, when he noticed pain in the epigastrium while at work. Later the pain increased in severity. He would experience fulness, pyrosis, nausea and distention about one-half to one hour after meals, the distress developing into a cramplike pain, often requiring gastric lavage. After a short rest his condition improved for a while. Since the past month, however, the symptoms have returned in greater severity: Pain almost continuously; hunger pain, somewhat relieved by food, coming on



one or two hours after meals. Is awakened between 3 and 5 A.M. with pain, burning, and sour regurgitations. Has to induce vomiting. Lost fifteen pounds.

A chemical examination of the stomach contents one hour after an Ewald test meal revealed a moderate amount of hypersecretion, 56 free HCl and 84 total acid, and a positive test for blood.

The roentgen examination at once revealed a stomach with a markedly exaggerated peristalsis, which came on in intermittent spasmodic seizures, causing violent antral contractions for several cycles. A penetrating ulcer the size of a 5-cent piece was seen in



FIG. 3.—Case II.

the pars media. The point of tenderness corresponded exactly under the fluoroscope to the crater on the lesser curvature. There was a marked duodenal irritation and very rapid evacuation. There was no retention beyond six hours. Suffice it to say this patient responded at once to treatment; all his symptoms abated and after four weeks he was free from all symptoms. He returned to work after a short while. About six months after the initial examination the patient was sent for and reexamined. He felt well and was able to eat more liberally, with but slight restrictions. He has gained in weight and has no tenderness in the epigastrium.

A roentgen-ray examination showed a complete absence of the ulcer on the lesser curvature. The peristalsis was much less intense, approaching more to normal.

Several subsequent examinations, the last one in January, 1921, showed a normal condition of the lesser curvature, and peristaltic waves were seen to pass over the entire lesser curvature. The acidity was reduced to 24 free HCl and 36 total acid.



FIG. 4.—Case II.

CASE III (Figs. 5 and 6).—R. I., male, aged forty-nine years, came under my observation in January, 1917. He complained that for many years past he had suffered from epigastric pain with variable remissions, at times spreading over a period of nine months, when he was totally free from symptoms. During the past five months he suffered daily from gastric distress, which came on regularly about one and a half hours after his meals. He would also be awakened at night, when he would use an enema and apply heat to the abdomen. He attributed all his complaints to constipation in view of the fulness and distention which developed during the attacks.

The roentgenological examination revealed a niche, about one-half inch in diameter, which was extremely tender to pressure.

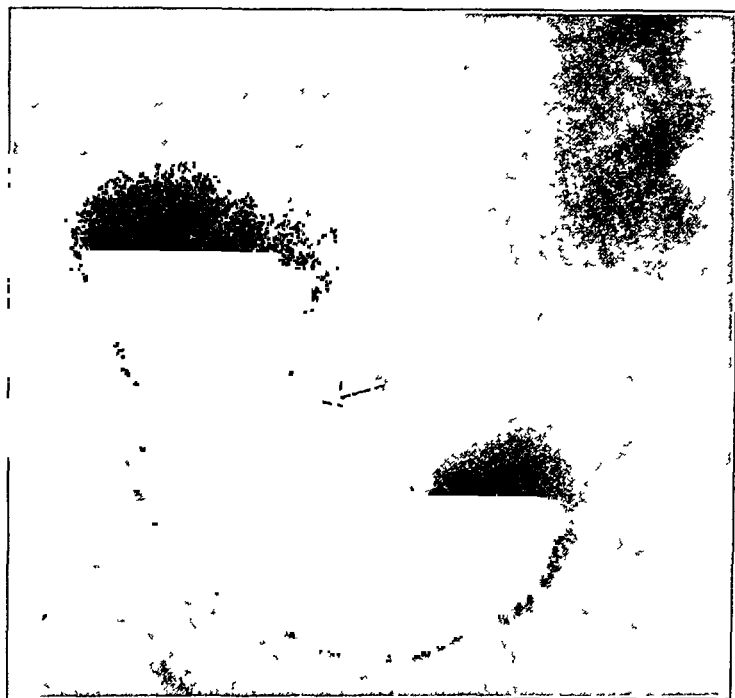


FIG. 5.—Case III.

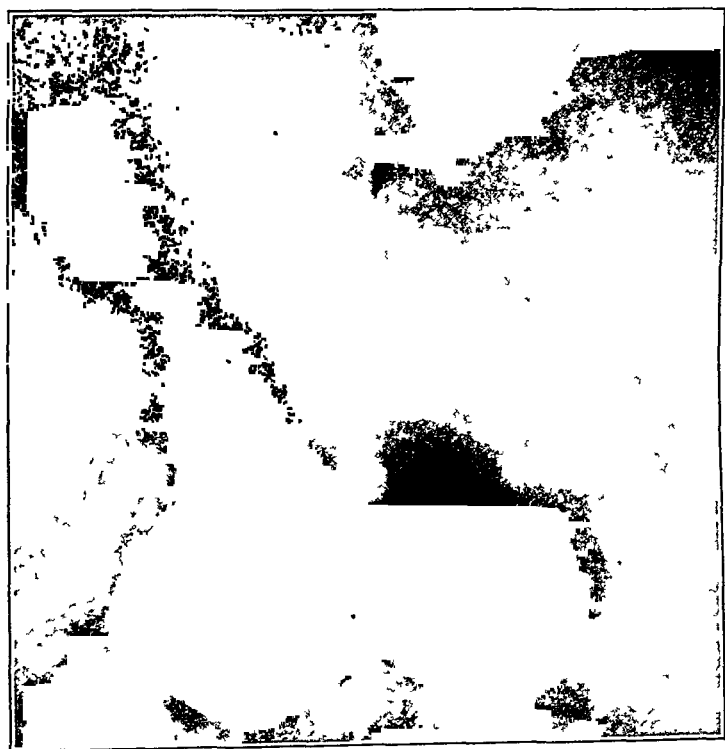


FIG. 6.—Case III.

He had 58 free HCl and 76 total acid. The routine treatment of a Lenhartz diet and rest in bed for a period of four weeks was carried out with the most gratifying clinical results.

The roentgenological examination carried out five months later failed to visualize the niche. When last seen he pursued his regular occupation, unmolested by the advent of previous interruptions. He continues to be guarded with his diet, excluding spices, sweets and red meats. The roentgenological examination in January, 1921, revealed an active lesser curvature with no trace of any indurated area. A chemical examination revealed an acidity of 38 free HCl and 54 total acid.



FIG. 7.—Case IV.

CASE IV (Figs. 7 and 8).—L. L., male, aged fifty-three years was taken from the Beth Israel Clinic. Presented several points of extreme interest. (1) Patient gave a definite ulcer-history dating back twelve or thirteen years, with periods of remission and seasonal exacerbations. When seeking relief at the clinic in 1918 the patient complained of intense pains both by day and by night and often had to induce vomiting to obtain relief. (2) Three different examinations during the same month were made by two different observers,

who found a large penetrating niche at the pars transversalis close to the incisura angularis. (3) The base of the niche presented an area of defective filling, strongly suggesting malignant degeneration of an old callous ulcer. (4) Surgery was advised by everyone connected with the case. The patient, however, objected strenuously to an operation. In fact, he placed little credence in our efforts, firmly believing that all his complaints were due to constipation. He therefore followed, but in a half-hearted way, the treatment suggested, mostly ambulatory. It nevertheless succeeded in alleviating his pains. We lost track of him for two years. On

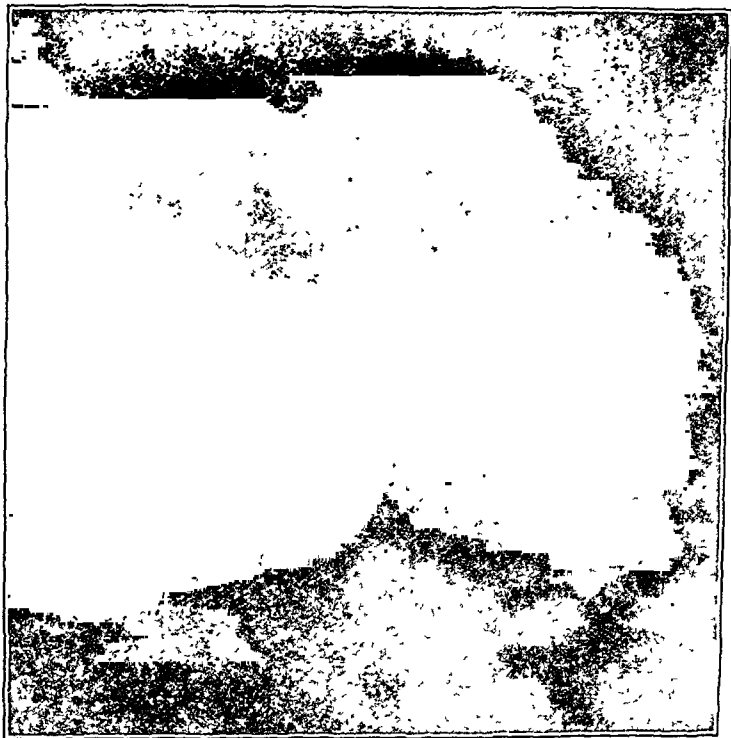


FIG. 8.—Case IV.

February 5, 1921, we located him and with great efforts we finally succeeded in overcoming his objection to a reëxamination. He felt absolutely well and refused to have anything to do with doctors.

At present his diet is far from guarded and he eats the coarsest of foods. He admitted, however, that at times he would experience heartburn. The examination on February 5, 1921, revealed a smooth and active lesser curvature. The peristaltic waves passed over evenly. No indurated areas could be traced. The striking feature in this case, however, was the violent peristaltic seizures over the entire body of the stomach. The stomach would appear

completely segmented into five different parts, with but slight remissions; the seizures under the fluoroscopic examinations would become almost continuous. Evidently the stomach still did exhibit a strong potentiality for the development of an ulcer. Even though his niche had disappeared the status of inherent muscular irritability was still strongly manifest.

CASE V (Fig. 9).—F. B., female, aged forty-four years, married, came under my observation October 14, 1919. She was referred by Dr. L. Greenwald with a history of epigastric pain dating back several years. The pain was more intense toward the left of the abdomen and was often referred to the back. The patient had a mitral presystolic murmur and a slightly palpable liver border. She was treated for years for her cardiac disease. All her



FIG. 9.—Case V.

pains were attributed to hepatic engorgement. The patient was apparently never quite totally free from pains, but said that at certain times she would have periods of exacerbation; when the pain was very intense it was almost unbearable. On close questioning it was elicited that her pains came on before meals and would be somewhat relieved by partaking some food. The pains, however, returned several hours later. After every meal they would persist into midnight, reaching such high intensity that a physician would be called in to administer a morphin injection. The patient had no nausea, pyrosis or vomiting, but eructated sour and bitter fluid. She lost considerable weight and looked very emaciated. Several physicians who saw her during these emergency night calls considered the case as one of cholelithiasis. The clinical picture, in fact, strongly warranted such a diagnosis. The roentgenological

examination at once revealed a penetrating ulcer in the vertical portion of the stomach on the posterior wall close to the lesser curvature. A definite point of tenderness was elicited corresponding exactly under the fluoroscope with the ulcer pocket. The acidity was 44 free HCl and 66 total acid. Hemoglobin, 70 per cent. Red blood cells, 4,500,000. The patient was put to bed and no food was taken by mouth for a period of three days, after which time a modified Lenhart diet was used. The improvement was slow. Nevertheless, during the second week the pains abated considerably and by the end of her treatment they had entirely disappeared. A reëxamination at the end of two months revealed a complete disappearance of the niche. During the past eighteen months the patient had two mild recurrences of gastric distress. They were never intense and passed over very quickly, after a short rest, which was advised especially on account of her cardiac condition. She is a hard-working housewife and is at no time any too careful with her food. Several examinations since at no time revealed any return of the niche. The last examination in January, 1921, revealed a smooth lesser curvature with normal peristaltic waves passing over the region of the ulcer. Her acidity went down to 26 free HCl and 34 total acid, although a moderate hypersecretion still persisted.

CASE VI.—E. F., widow, aged fifty-five years, came under observation in February, 1920. The husband recently died from carcinoma of the tongue. She gave a history of pain and pressure in the upper abdomen for various periods as far back as three or four years. The pains would come on in very severe attacks, which would last for a few hours for one day and would then let up gradually and would continue in a milder form for a number of weeks, after which time they would totally disappear for several months. The last attack commenced about a month ago, while attending to her husband when *in extremis*. Contrary to her previous experiences there seemed to be no let up to this attack, for it seemed to persist and increase in severity. On close questioning the patient admitted that she always took a glass of hot milk for her pains and would then feel relieved for a short time. Otherwise the pains were not very regular. They would come on at night, requiring the application of a hot-water bag, and once necessitating a hypodermic of morphin. When intense they would be referred to the left of the abdomen and to the back. This patient was likewise treated for cholelithiasis and was advised operation. The roentgenological examination promptly revealed a "Haudeck niche" in the midgastric region. Her acidity was 44 free HCl and 66 total acid. Hemoglobin, 74 per cent. Treatment was carried on as in the previous cases and the patient made a slow but uneventful recovery. A reëxamination three months after showed a total disappearance of the niche. Another examination in January,

1921, revealed a slight indentation at the site of the ulcer, with the faintest possible suspicion of hour-glass formation. The patient is free from all symptoms. Her acidity went down to 26 free HCl and to 34 total acid.

Further observations will be necessary to watch if an hour-glass ever develops in the process of scar contraction.

CASE VII.—R. L., aged forty years, the third female of this series, came under observation in November, 1919. She gave a less complicated but a rather definite ulcer-history with pains associated with the intake of food, and a good appetite, but with a fear of eating. Had occasional vomiting attacks about two and a half hours after a meal, when the intensity of the pain reached its height. Had one attack of pain and vomiting after midnight during the past week. The vomitus was strongly sour. Lost some weight. Patient said she was free from pain when she did not eat.

As in the previous cases the pain was referred to the left side and to the back, and there was a similar point of tenderness corresponding to the niche. Her acidity was 30 free HCl and 58 total acid. The roentgen-ray revealed a niche about one-half inch in depth by one-third inch in width. A similar plan of treatment was carried out. The niche completely disappeared within seven weeks, and now the patient has been free from symptoms since November, 1919. A recent reëxamination shows a restoration of the lesser curvature to a normal state.

CASE VIII.—S. S., aged fifty-seven years, was referred by Dr. S. Ehrlich on April 23, 1920. The patient complained of cramps for the past year, on and off, but more severe of late. They came on usually about two hours after meals and would continue for several hours. Was often awakened with pains after midnight and would be distressed until dawn. During the course of the pains he would apply heat to the abdomen, drink some milk or tea and would use an enema. He also complained of attacks of dizziness and constipation, these, however, having no relation to his gastric pains. He had many bad teeth and a mouthful of bridge-work. The patient also mentioned that thirty years ago he suffered with abdominal pains, for which he consulted a physician, but does not remember any details.

The roentgenological examination revealed a rather large atonic type stomach with a large overhanging "magenblase," which caused partial eventration of the left diaphragmatic dome. A layer of secretion, three fingers high, was seen to overly the contrast meal, indicating a large fasting secretion. Peristalsis was generally diminished, but occasionally the stomach was thrown into violent peristaltic seizures, quickly, however, tiring and returning to the previous state. The pylorus was spastic. At the midportion of



the lesser curvature a small elevation was noted, which was constant during all the fluoroscopic and roentgenological examinations. A point of tenderness was present over this area. The antral portion appeared rotated toward the left to the ulcer-bearing area, giving the impression of the Schmeiden tobacco-pouch or snail-form stomach, a purely spastic and protective mechanism.

The fasting secretion was large, containing bile, occult blood and a moderate acidity. After an Ewald test meal the acidity reached up to 40 free HCl and 60 total acid. The contents were in a high degree of chymification. Hypersecretion was marked. A reëxamination on February 7, 1921, revealed a disappearance of the niche. The stomach had returned to its normal size, was no longer atonic, exhibiting at times violent and continuous peristaltic contractions. The acidity was reduced to 30 free HCl and 46 total.

CASE IX.—I. G., grocer, aged forty-nine years, was referred by Dr. Glanz on January 31, 1920. The onset of his complaint began only about one month ago, when he began to experience left-sided abdominal pains rather indefinitely associated with meals. He noticed that his pains would be more severe when he did hard manual work such as lifting his wares and when exerting himself in walking. During the past two weeks he vomited almost every day during the height of his pains, after which he felt relieved. He lost a great deal in weight. The gastric contents revealed a hyperacidity of 42 free HCl and 64 total acid and considerable mucus.

The roentgenological examinations revealed a fairly large penetrating ulcer close to the incisura angularis, measuring three-quarters of an inch in width and one-third of an inch in depth. It was tender to pressure. Under the fluoroscope a deep spastic incisura was seen on the greater curvature corresponding.

A reëxamination in December, 1920, revealed active lesser and greater curvatures. No trace of the niche or induration was to be seen.

CASE X.—II. S., male, aged forty-eight years, umbrella-maker, came under observation in November, 1919. He presented a history of abdominal pain occurring on and off during the past six years. The last attack is continuous for the past two months and is characterized by considerable gastric distress, intense heartburn, nausea and water-brash. Takes bicarbonate of soda, which gives him some relief. At night the distress is at its height and he is forced to induce vomiting, the vomitus often containing food eaten on the previous day. His appetite is very poor during the attacks. Has especially no desire for meats. Takes liquid foods, such as milk, because they alleviate his distress. Lost twenty pounds.

The roentgen examination revealed an atonic type stomach lying

low, with flaccid gastric musculature. At times, however, the stomach would contract violently, the contraction persisting for an unusually long time in a spastic state, after which it would relax, returning to its previous flaccid and atonic form. On the lesser curvature, close to the incisura angularis, a small niche was noted. It was tender on deep pressure. The gastric motility was considerably disturbed, a fairly large retention still persisting after eighteen hours.

The gastric acidity at the one-hour period was 12 free HCl and 40 total acid, rising in the second hour to 50 free HCl and 68 total.

The routine treatment was carried out and the patient was kept in bed for five weeks.

His symptoms have been so far gradually abated and he has been free from all gastric disturbance up to the present time of writing.

The niche has completely disappeared. The stomach has become reduced to normal size and returned to normal motor function.

CASES XI AND XII.—I. S. and M. L., wage-earners, present considerable similarity in the duration and manifestations of their symptoms. Both are forty-five years of age. One applied for treatment on January 13, 1920, and the other on February 8, 1920. The symptoms were rather characteristic of ulcer. The pains would come on about one and one-half to two hours after meals and would invariably be referred to the left side and back. Lying down would ease their discomfort. Taking of alkalis or food would invariably stop the pain, which would return again after two hours. The chemical examination in I. S. was 42 free HCl and 60 total acid, and in M. L. 54 free HCl and 74 total acid.

The roentgenological examination revealed a penetrating ulcer in each case, situated close to the junction between the vertical and horizontal portions of the stomach. In both tenderness on deep pressure was elicited. There was no disturbance in motility. After four weeks of treatment in each case the symptoms completely disappeared and have not returned.

A reëxamination three months later and again during February, 1921, revealed a smooth and even lesser curvature. During the last examination peristaltic waves were seen to pass over.

CASE XIII.—H. H., aged thirty-three years, merchant, was referred by Dr. J. Block July 16, 1920. He gave the following very interesting history: Seven weeks ago, while motoring at night, he met with an accident. He sustained no injury, but was consequently exposed to a cold spring night between the hours of 11 P.M. and 3 A.M., in the open country, with little protection in the way of covering. When he reached home he complained of nausea, distress and pain in the upper abdomen. This lasted for

two weeks, with but slight hourly remissions. Felt apparently well for another two weeks, when the pain returned with greater violence, usually during the hours of 11 A.M., 3 P.M. and 1 A.M. Does not vomit, although nauseated. Bicarbonate of soda promptly gives him relief. Appetite is poor. Always takes some food when pain comes on, which gives him relief.

He characterizes his pains as a sensation of considerable distress and heartburn and accompanied by a feeling of fulness, pressure and distention, causing him to loosen his trousers belt. He then takes soda, after which he belches and is then relieved. Pains are not referred to the back but to the right iliac region.

The gastric contents' examination revealed a hypersecretion and a hyperacidity of 48 free HCl and 60 total acid at the end of the first hour, which came down to 15 free HCl and 24 total acid at the end of the second hour.

Roentgenologically a penetrating ulcer was found on the lesser curvature at the incisura angularis nearer the anterior wall. The pocket measured about one-half inch in width and one-third inch in depth. This area was very tender. The duodenum and pylorus were spastic.

Gastric motility was delayed, about one-quarter of the contrast meal being retained at the end of six hours. Hypersecretion could be seen both in the retention plate as well as in the fasting stomach before and after the administration of the barium meal. Careful treatment was applied, the patient remaining in bed for three weeks, after which time a stay at a summer resort for another few weeks was carried out. A reexamination eight weeks later showed a total absence of the niche. The patient continues to feel in the best of health, with but few dietary restrictions.

CASE XIV.—S. F., aged fifty-one years, was taken from the Beth Israel Hospital. Came under observation during November, 1920. The history was of rather short duration and characterized by left-sided abdominal pains referred to the back, aggravated by food and manual labor. The gastric acidity revealed 24 free HCl and 50 total acid.

The roentgenological examination showed a large niche, measuring about one inch in diameter, situated at about the incisura angularis. The patient was treated at the hospital. One month later a reexamination revealed the ulcer receded to about one-quarter its original dimensions. Another examination after one more month revealed the ulcer crater entirely gone, leaving an indurated area. The peristaltic wave was not seen to pass over the induration.

From a study of these cases it appears indisputable that gastric ulcer may be healed. The evidence for this is the following: (a) Absence of symptoms, (b) disappearance of niche, (c) passage of peristaltic waves.

The following questions, however, immediately arise:

1. Can we regard these cases, three of which have been free from all symptoms for a period extending over four years, as permanently cured, or are these simply longer remissions such as one might see occurring in the life-history of any ulcer case—the so-called temporary cure?

2. What constitutes a permanent cure?

3. Can a peptic ulcer be permanently cured?

Are we seeing but a phase in the life-history of the ulcer? Is the retrogression stage of the niche analogous to the remission stage of the ulcer when the symptoms abate for a shorter or longer period only to recrudescence after an alimentary debauché or other disturbing factors? Does healing of the ulcer, which consists of filling in with granulations, scar formations, with retraction of its base so that the gastric surface becomes smoothened and no defect in the contour of the stomach is visualized? Does this process of regeneration take place during every so-called remission stage and may this break down again during the recrudescence period? Does the regeneration process go on only in those cases leading to permanent cures? Therein lies the entire key to the solution. If we can prove upon further observation the reappearance of the niche in the same location as before, then we cannot hold these as permanent cures, but merely an event in the process of breaking down and repair which goes on with fairly definite regularity, occasionally seasonal, one event following another in the life-history of the ulcer. As may be seen, however, the cases herein reported have not so far shown a reappearance of the niche. Repeated roentgenological examinations have failed to visualize the previous or any other niche. While occasionally some of the cases have come back with slight gastric distress, these symptoms have passed over quickly, never resuming the course of the initial attack and never exhibiting the typical ulcer syndrome. Perhaps one might say that the gastric ulcer runs a course somewhat different than the duodenal ulcer. In the latter cases time and again the patients do come back with a similar train of symptoms, necessitating the usual rest and a resumption of a restricted diet, often a new Lenhartz regimen.

Clinically one might assume a cure when the patient has remained free from the symptoms for a period of several years, has gained in weight and has been on a liberal diet. Moynihan claims that even a lapse of three years would suffice to consider a case as permanently cured. One meets, however, incidentally with patients who give a clear ulcer history dating back many years with a long intervening period of remission. In our own experiences we note one case which gave an ulcer-history, thirty years ago, requiring medical attention. Three other cases revealed, in spite of the absence of the niche, an increased irritability of the gastric musculature, the stomach going into violently spasmodic contractions never seen in a normal state.

These patients complain at times of heartburn and continue with hypersecretions. One feels while examining these patients that they still retain a strong potentiality for gastric ulcer even though none be visualized during the reexamination.

We are therefore confronted with uncertainties and feel that a much longer period must elapse before considering these as permanently cured.

Regarding the subject from the etiological viewpoint the question whether ulcer is ever a curable disease becomes extremely difficult for a satisfactory reply.

While a definite etiological factor has yet not been established, still the most plausible theory is the neurogenic "or the spasm" theory. It is a common experience to meet ulcers in individuals presenting constitutional anomalies, and the tendency is to attribute these anomalies to the instability of the autonomic nervous system. These are characterized in part by the irritability of the neuromuscular apparatus of the stomach, manifesting itself in hyperkinetic and hypersecretory phenomena such as increased peristole, deep segmenting antral peristaltic waves, gastrospasm, increased intragastric tension and high acidities.

One can readily see how an abrasion occurring in the mucous membranes of the stomach in these individuals, such as may arise from a coarse food particle, may lead to the formation of a peptic ulcer. The increased muscular tension and the constant grinding of a hyperacid chyme against such an abrasion supply sufficient causative agents for the developing of ulcer.

The endocrine dyscrasias such as adrenalin insufficiency, acting either alone or through the thyroid gland, may exert a biological influence on the autonomic nervous system, producing similar constitutional anomalies susceptible to the production of ulcer.

Bearing in mind these constitutional etiological factors, can we assume that by causing the disappearance of the niche through temporary rest and diet we can as well change the susceptibility or predisposition of the individual?

The so-called vagotonic status continues to persist even after the cure. The neurogenic secretory and motor disturbances continue to exert their baneful influences. One cannot expect to cure a status with diet, not even with a resection of the ulcer. New ulcers may form at different locations. If we could succeed in altering the underlying etiological status, only then might we hope to achieve a permanent cure.

The process of healing consists not only in the organic changes in the niche, but also in the disappearance of symptoms, and chiefly that of pain. The success of the healing process and the disappearance of the symptoms are due mainly to allaying and stabilizing the irritability of the vegetative nervous system. The former process goes hand in hand with the latter and is dependent upon it. The

first factor occurring in the process of healing is the inhibition of spasm. Of this we have definite proof in the roentgen and Rehfuess studies of food rest. With each subsequent examination we note a gradual diminution in the size of the retention until it totally disappears. Friedman and Hamburger<sup>7</sup> in their experimental ulcers have shown that one can delay the healing of ulcers in dogs when pyloric obstruction is induced. Ordinarily such ulcers with unimpaired gastric motility would heal within eight to ten days, whereas with an accompanying ligation of the pylorus the healing could be retarded almost indefinitely. Therefore with the improvement of motility in man healing of the ulcer is enhanced.

The cessation of the symptoms is likewise dependent upon the disappearance of spasm. Hertz,<sup>8</sup> Carlson,<sup>9</sup> Rogers and Hardt,<sup>10</sup> Ginsburg, Tumpowsky and Hamburger<sup>11</sup> have all shown that pain is due to increased tension of the gastric musculature which is brought about by an increased state of irritability from stimuli, whether from within, such as the effect of the hyperacid secretion on the sensory nerves situated on deeper strata of the ulcer-bearing area and so causing increased tonicity, increased contractibility and increased tension, or from extrinsic causes through the viscerosensory reflex.

Rest, avoidance of mental strain, a restricted non-irritating diet, the atropin group are all conducive to stabilizing the autonomic nervous system, and the disturbed motor phenomenon of gastrospasm is the first disorder to disappear.

It is not so, however, with the secretory apparatus. The healing of the ulcer goes on independently of the character of the secretion, for this remains unaltered in the majority of cases. The painstaking work carried on by Crohn and Reiss<sup>12</sup> at the Mount Sinai Hospital in a series of 34 cases showed that the chemistry of the secretion, as well as hypersecretion, remained unchanged even though there was a complete cessation of the symptoms and a marked improvement of the patient. Out of the 34 cases of hyperacidity, 21 remained high in spite of active treatment, 62 per cent showed a marked improvement even though they persisted with a high acid chyme. Out of the same series 50 per cent of the clinically improved cases showed a lessening in the amount of the secretion. The remaining 50 per cent continued with persistent hypersecretion, though subjectively the pain and pyrosis had disappeared. This further illustrates the inability to totally subdue the abnormal

<sup>7</sup> Experimental Chronic Gastric Ulcer, Jour. Am. Med. Assn., February, 1917.

<sup>8</sup> The Sensibility of the Alimentary Canal, London.

<sup>9</sup> Epigastric Pain, Am. Jour. Physiol., 45.

<sup>10</sup> Am. Jour. Physiol., 38, 274.

<sup>11</sup> Contribution to the Physiology of the Stomach, Jour. Am. Med. Assn., September 30, 1916.

<sup>12</sup> Effects of Restricted (So-called Ulcer) Diets upon Gastric Secretion and Motility, Am. Jour. Med. Sc., January, 1920.

stimuli exerted upon the secretory fibers. Their persistence gives added proof of a continued state of ulcer predisposition.

Any psychic disturbance may at once incite a retrograde process and cause disturbed motor functions. Symptoms may occur even without the presence of an ulcerated area and are probably due to psychic disturbances. This explains the occasional reappearance of symptoms even in the absence of a visible niche.

**Surgical Indications.** Assuming, then, that ulcer is a constitutional disease, gastric surgery can only be employed in the method analogous to the amputation of a leg in diabetic gangrene. It cannot obliterate the primary etiological factor, but removes a diseased area, a localized pathological manifestation of a systemic condition; for how then can one explain the postoperative recurrence of such ulcers? Marginal ulcers were at first considered to be due to a persistent silk suture in the gastrojejunostomy stoma and later to trauma inflicted by clamps in the course of operation. This does not, however, explain the occurrence of jejunal ulcers which may be an inch or more away from the point of anastomosis. Often a subsequent operation of complete excision of the old anastomotic area and a new gastrojejunostomy results shortly in a recurrence of the previous picture. Such experiences can be multiplied in the annals of the most eminent surgeons, and we can learn from their frank admissions of the complexity of this problem, where in spite of the greatest technical skill employed failure is often encountered. In one of my cases in which a primary operation was first performed for a chronic, profusely bleeding, recurring duodenal ulcer, necessitating another surgical intervention, a partial gastrectomy and a new gastrojejunostomy were performed. Shortly after, however, a third ulcer had appeared high up along the lesser curvature in the remaining gastric pouch, a penetrating ulcer situated considerably away from the point of anastomosis. One cannot describe the intense physical distress in this man with a mutilated organ, perverted physiology and above all the recurrence of his initial lesion.

If surgery is not conducive to permanent cures, and if simple medical treatment brings about a disappearance of the niche and symptoms, it behooves us to employ medical therapy in all cases that are compatible with a restoration to normal morphology and function.

Surgery must be resorted to when the pathological process is beyond repair by conservative measures. It has its definite indications as follows:

1. One need not mention acute perforations, for here prompt surgical intervention is a life-saving device.

2. Chronic perforating ulcers in which a communication of the lumen of the stomach with the neighboring tissues have been made, causing a separate small gastric pouch or sac. These can easily be differentiated roentgenologically by the overhanging gas bubble.

No attempt should be made to submit such cases to medical treatment, for no one can foretell when an acute perforation will supervene; also where communication has been established with neighboring hollow viscera.

3. In all chronically recurring bleeding ulcers.

4. In hour-glass contractions where there is a tendency to narrowing of the connecting isthmus.

5. Those cases with frequent recurrence of symptoms in which repeated dietetic courses are required which admit the failure of controlling the symptoms by medical means.

6. Too long a time must not be spent with intense medical treatment if symptoms do not abate.

**Summary.** 1. A series of 14 cases of gastric ulcer is reported in which complete healing of the ulcer was obtained by medical treatment and has been maintained for periods up to four and a half years.

2. The question whether these ulcers have been permanently cured is discussed and their possible relationship to constitutional states in regard to etiology and recurrence pointed out.

3. The conditions which determine whether medical treatment is to be replaced by surgical interference are described.

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## A MICRO-METHOD FOR THE DETERMINATION OF SUGAR IN SMALL AMOUNTS OF BLOOD.

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BLOOD-SUGAR determinations are of practical value in the diagnosis and control of certain diseases of metabolism. As indicated by Allen<sup>1</sup> and Williams<sup>2</sup> this applies particularly to diabetes.

The value of blood-sugar determinations, however, is largely dependent upon their degree of accuracy, for faulty determinations are worse than useless, as they may lead to erroneous conclusions. Many methods and modifications have been introduced. In this country the colorimetric methods of Lewis and Benedict<sup>3</sup> and of

<sup>1</sup> Total Dietary Regulation in the Treatment of Diabetes, Monograph No. 11, Rockefeller Institute for Medical Research, 1919.

<sup>2</sup> The Clinical Significance of Blood Sugar in Diabetes Mellitus, Arch. Int. Med., 1919, 23, 546.

<sup>3</sup> A Modification of the Lewis-Benedict Method for the Determination of Sugar in the Blood, Jour. Biol. Chem., 1918, 34, 203.



Folin and Wu<sup>4</sup> are largely employed. Although only a small quantity of blood (usually 2 cc or more) is required for these methods it is necessary to obtain it from a vein.

There is no serious objection to venous puncture ordinarily, but at times it is difficult or undesirable, particularly when determinations are made on children or repeated determinations on adults.

To overcome the necessity for venous puncture, attempts have been made to adapt many of the blood-sugar methods to smaller volumes of blood which can be drawn from the finger tip or lobe of the ear. From the standpoint of accuracy such micro-modifications have not been found very satisfactory.

The method to be described is an adaptation of that of Folin and Wu to 0.2 cc of blood drawn from the finger or lobe of the ear by simple puncture. We have found it of value in supplementing the original method in cases in which it is desirable to avoid repeated venous puncture, and have obtained accurate and reliable results as judged by control determinations by the Folin-Wu method. One advantage of the method is that the final colorimetric comparison can be made in any accurate type of colorimeter.

**Solutions.** No change has been made in the reagents used in the original method of Folin and Wu, and this obviates the necessity of preparing a separate set of solutions. The directions for their preparation, taken from the paper of Folin and Wu, are included here merely as a matter of convenience.

1. *Alkaline Copper Solution.* Dissolve 40 gm. of pure anhydrous sodium carbonate in about 400 cc of water and transfer to a liter flask. Add 7.5 gm. of tartaric acid, and when the latter has dissolved add 4.5 gm. of crystallized copper sulphate. Mix and make up to a volume of 1 liter. If the chemicals used are not pure a sediment of cuprous oxide may form in the course of one or two weeks. If this should happen, remove the clear supernatant reagent with a siphon or filter through a good quality filter paper. The reagent seems to keep indefinitely. To test for absence of cuprous copper in the solution, transfer 2 cc to a test tube and add 2 cc of the molybdate phosphate solution; the deep blue color of the copper should almost completely vanish.

2. *Molybdate Phosphate Solution.* Transfer to a liter beaker 35 gm. of molybdic acid and 5 gm. of sodium tungstate. Add 200 cc of 10 per cent sodium hydroxide and 200 cc of water. Boil vigorously for twenty to forty minutes so as to remove nearly the whole of the ammonia present in the molybdic acid. Cool, dilute to about 350 cc and add 125 cc of concentrated (85 per cent) phosphoric acid. Dilute to 500 cc.

3. *A 10 per cent solution of sodium tungstate.*

<sup>4</sup> A System of Blood Analysis. Supplement I. A Simplified and Improved Method for the Determination of Sugar, Jour. Biol. Chem., 1920, 41, 367.

4. *A two-thirds normal solution of sulphuric acid.*

5. *Standard Sugar Solutions.* Three standard sugar solutions should be on hand.

(a) A stock solution, 1 per cent dextrose or invert sugar, preserved with xylene or toluene. Dissolve 1 gm. of pure anhydrous dextrose in water and dilute to a volume of 100 cc. Mix, add a few drops of toluene or xylene and bottle. If pure dextrose is not available a standard solution of invert sugar made from cane sugar is equally useful. Transfer exactly 1 gm. of cane sugar to a 100 cc volumetric flask; add 20 cc of normal hydrochloric acid and let the mixture stand overnight at room temperature (or rotate the flask and contents continuously for ten minutes in a water-bath at 70° C.). Add 1.68 gm. of sodium bicarbonate and about 0.2 gm. of sodium acetate to neutralize the hydrochloric acid. Shake a few minutes to remove most of the carbonic acid and fill to the 100 cc mark with water. Then add 5 cc more of water (1 gm. of cane sugar yields 1.05 gm. of invert sugar) and mix. Transfer to a bottle, add a few drops of xylene or toluene, shake well and stopper tightly. The stock solution made in either way keeps indefinitely.

(b) A solution containing 1 mg. of sugar per 10 cc (5 cc of the stock solution diluted to 500 cc.).

(c) A solution containing 2 mg. of sugar per 10 cc (5 cc of the stock solution diluted to 250 cc.).

The diluted solution should be preserved with a little added toluene or xylene; it is probably better not to depend on such diluted solutions to keep for more than a month.

**Description of the Methods.** Using an accurately calibrated pipette obtain 0.2 cc of blood from the finger tip or lobe of the ear. Deliver the blood into a centrifuge tube containing 3.8 cc of water. Rinse out the blood in the pipette by drawing the water up and allowing it to run out several times, and finally blowing out thoroughly. The total volume in the centrifuge tube should now be 4 cc (3.8 cc of water and 0.2 cc of blood). Stir with a very thin glass rod to ensure thorough laking of the blood. Add 0.5 cc of the 10 per cent solution of sodium tungstate and stir. Add 0.5 cc of two-thirds normal sulphuric acid. Stopper the tube tightly and shake vigorously. Remove the stopper and centrifugalize. Pipette off 3 cc of the clear solution and transfer to a Folin blood-sugar test tube. Add 2 cc of standard sugar solution containing respectively 0.2 and 0.4 mg. of dextrose to two similar tubes. Add 1 cc of water to each standard to bring the total volume to 3 cc or equivalent to that of the unknown. Add 2 cc of the alkaline copper solution to each tube.

This makes the total volume 5 cc as compared with 4 cc in the original Folin method. It is therefore necessary to use tubes having a slightly larger bulb, so that when containing 5 cc the surface of the solution comes within the constricted portion of

the tube. They may be made from ordinary test tubes, as described by Folin, or from the regular blood-sugar tubes by blowing out the bulb slightly. In addition the tubes should be marked at 12.5 cc and 25 cc.

Place the tubes in a boiling water bath and heat for six minutes. Transfer to a cold water bath and let cool, without shaking, for two or three minutes. Add 2 cc of the molybdate phosphate solution to each tube. Let stand at least two minutes until all of the cuprous oxide is dissolved. Dilute the unknown with water to the 12.5 cc mark and the standard tubes to the 25 cc mark. Close with rubber stoppers, mix and transfer to colorimeter cups. Make the comparison in the usual way, using the standard that comes within the closest range of the unknown. Avoid bubbles which tend to accumulate on the bottom of the plungers. Before comparing the unknown of course the standard should be read against itself to check the adjustment of the colorimeter.

In making the calculation it should be noted that the unknown is diluted to 12.5 cc while the standards are diluted to 25 cc. The standards used are therefore equivalent to 0.1 and 0.2 mg. of dextrose respectively instead of 0.2 and 0.4 mg., as in the original Folin method. These standards cover the range of blood sugars between about 60 and 220 mg. per 100 cc. For higher concentrations the unknown should also be diluted to 25 cc and compared against the stronger standard, in which case the standard has the same value as in the original Folin method, namely, 0.4 mg. of dextrose. By roughly comparing the unknown with the standards just before dilution one can determine whether the unknown should be diluted to 12.5 cc or 25 cc to come within the range of the standards.

The 3 cc of solution taken for analysis represents three-fifths of 0.2 cc or 0.12 cc of whole blood. Therefore the calculation is made as follows, remembering, however, to use the proper value for the standard depending upon whether the unknown is diluted to 12.5 cc or 25 cc:

$$\frac{\text{Reading of standard}}{\text{Reading of unknown}} \times \frac{\text{mg. dextrose in standard}}{1} \times \frac{100}{0.12} = \text{mg. dextrose in 100 cc blood.}$$

**Discussion.** The method described above is identical in principle and very similar in technic to the method of Folin and Wu. In fact, we have attempted to adhere as closely as possible to the original method and the variations are due to the smaller volume of blood taken for analysis. Before introducing these changes it was necessary first to check their effect on the accuracy of the determination.

In the precipitation of the blood proteins different proportions of blood and reagents are used. The original proportions might possibly be preserved—that is, 0.2 cc of blood, 1.4 cc of water,

0.2 cc of tungstate and 0.2 cc of acid, giving a total volume of 2 cc, from which after centrifugalizing difficulty is encountered in obtaining even 1 cc of solution for analysis. To ensure an adequate volume of liquid for examination we have increased the total volume to 5 cc, which, after centrifugalizing, yields 3 cc for analysis. In doing so we have preserved the original concentration of tungstate, but at the same time the total amount in the portion taken for analysis is slightly increased. That this slight increase in tungstate is not sufficient to effect the determination is indicated by the following table:

TABLE I.—RESULTS OBTAINED WITH FOLIN-WU METHOD  
AND MICRO-MODIFICATION.

Blood No.	Folin-Wu, per cent.	Micro-modification, per cent.
1	0.0588	0.0570
2	0.0843	0.0850
3	0.0913	0.0925
4	0.0950	0.0960
5	0.0970	0.1090
6	0.1040	0.0985
7	0.1110	0.1140
8	0.1140	0.1170
9	0.2100	0.2000
10	0.2200	0.2240

The table also shows the degree of accuracy of the method as compared to that of Folin and Wu.

It was also necessary to establish the reducing value of the copper solution to the smaller amounts of sugar encountered in using 0.2 cc of blood and also to the change in concentration due to taking 3 cc instead of 2 cc of filtrate for analysis. Working with pure sugar solutions and using the technic of the micro-modification we have covered the range of blood sugars ordinarily encountered. Very good results were obtained, as shown by the following table:

TABLE II.—RESULTS OBTAINED USING PURE DEXTROSE SOLUTIONS OF  
CONCENTRATIONS ORDINARILY ENCOUNTERED IN THE EMPLOY-  
MENT OF THE MICRO-MODIFICATION.

Theoretical blood sugar, per cent.	Amount of dextrose in 3 cc of filtrate, mg.	Amount of dextrose by analysis, mg.
0.06	0.072	0.075
0.07	0.084	0.083
0.08	0.096	0.098
0.09	0.108	0.106
0.1	0.12	0.125
0.11	0.132	0.138
0.12	0.144	0.149
0.13	0.156	0.152
0.14	0.168	0.170
0.15	0.180	0.176
0.20	0.240	0.242
0.25	0.300	0.305
0.30	0.360	0.364
0.35	0.420	0.410

Before using the modification suggested the paper of Folin and Wu should be carefully read, all precautions noted and finally a series of duplicate determinations made to check the accuracy of the micro-modification with the original method.

In case a number of determinations are desired on patients in the hospital the centrifuge tubes, containing 3.8 cc of water, may be prepared in the laboratory and carried to the bedside, the various bloods taken, transferred to the tubes and finally returned to the laboratory for analyses.

**Conclusions.** 1. A micro-modification of the method of Folin and Wu is described for the determination of blood sugar in 0.2 cc of blood, which may be obtained from the finger or lobe of the ear.

2. We have found the method of value for clinical purposes in supplementing the original method when blood cannot be obtained from a vein.

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## THE ROLE OF CONCENTRATED CEREAL-MILK MIXTURES IN EARLY INFANCY.

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THE activity of diastatic and amylolytic ferments in the digestive functions of the newborn has long been recognized. It has been noted, moreover, that even in the first days of life there is a rapid increase in power to digest starch. This capacity is highly developed by the eighth month and is said to undergo little increase during the succeeding two years.<sup>1</sup> Due attention has been paid to the infant's apparent need for cereal to supplement milk during the last months of the first year, and the addition of barley or other similar finely divided cereal to the formula by the third month, at least, has been customary. Foremost reasons for this practice have been the protective colloid action of the cereal, notably barley, in ensuring advantageous subdivision of casein curds; and the comparatively slow breaking down and absorption of starch in a manner not conducive to the fermentation so noticeable at times when carbohydrate of less complex molecular structure is employed exclusively.

Notwithstanding these facts the administration to very young infants of gruel mixtures of almost solid consistency, containing 10 to 15 per cent starch, is a comparatively new departure and

<sup>1</sup> Morse and Talbot: Diseases of Nutrition and Infant-feeding, Chapter III.

calls for the setting down of additional clinical data as rapidly as these become available.

Hans Hahn,<sup>2</sup> in 1911, reported good results from the administration to vomiting infants of 5 to 6 per cent grits in milk in such form that 1 liter represented 1000 calories.

McClure,<sup>3</sup> in 1914, reported the case of an infant who retained breast milk, but after three and a half months uniformly regurgitated artificial food and at six and a half months weighed only 7 pounds, 10 ounces, giving evidence that the vomiting was neurotic. Immediate cessation followed the feeding of thick barley gruel with a spoon, and recovery continued, the stools remaining starch-free, on the substitution of a thick mixture of farina and milk (1 to 6) boiled one hour.

The most striking pioneer work was that of Sauer,<sup>4</sup> who in 1918 reported 12 cases of pyloric obstruction treated by thick cereal, with 11 recoveries and 1 death from subsequent pneumonia. Two of his patients were successfully given the thick cereal feeding at five weeks and one month respectively, each weighing about 5 pounds. The mixture consisted of 9 ounces of skimmed milk, 12 ounces of water, 6 tablespoonfuls of farina and 3 tablespoonfuls of dextrimaltose, boiled one hour in a double boiler until sufficiently thick to adhere to a spoon and fed to the amount of at least 2 tablespoonfuls six or seven times in twenty-four hours. Sauer believed that the thick cereal could not be ejected by the sudden explosive contractions that produced projectile vomiting of liquid and that the effect of the thick food under slow peristaltic contraction of the gastric wall was gradually to relax the constriction of the pylorus.

Porter<sup>5</sup> a year later reported similar success with 10 cases, any one of which he would have submitted otherwise to operation with confidence of finding "a definite hypertrophy of the pyloric mucosa with obstruction at the outlet of the stomach." In preference to the farina he employed 10 per cent rice flour as more soluble under moderate heat and less likely to cause diarrhea through saccharolytic fermentation. The food, partially liquefied, was fed into the base of a "Hygeia" nipple, which was slit at the end, thus permitting sucking. One of his patients was five weeks old and weighed 6 pounds.

The method was further employed by Mixsell,<sup>6</sup> with striking success, in cases of malnutrition dependent on vomiting. He was able to combine cane sugar, maltose and rice or farina, with skimmed milk ranging from 1 to 2 per cent fat, in a very thick and yet apparently readily digestible mixture with a "polycarbohydrate" content

<sup>2</sup> Med. Klin., 1911, 7, 1452.

<sup>3</sup> Am. Jour. Dis. Children, 1914, 7, 48.

<sup>4</sup> Arch. Pediat., July, 1918, p. 385.

<sup>5</sup> Ibid., 1919, p. 385.

<sup>6</sup> Ibid., August, 1919, p. 449, and August, 1920, p. 486.

as high as 16 per cent. The resulting gains were spectacular: in one instance, 82 ounces in seventy days; in another, 68 ounces in eight weeks; and in another, 110 ounces in eighty-six days. After the sixth month he employed from 2 to 6 ounces of green vegetable purée with the cereal mixture, and concluded that in such form food high in carbohydrate percentage and of very high caloric value could be given beneficially, in malnutrition cases with disturbed digestion.

Recently, Durand<sup>7</sup> has reviewed 50 cases fed by him on thick cereal mixtures, including the records of infants ranging in age from three weeks to nine months and in weight from  $4\frac{3}{4}$  pounds up. Of 11 infants showing signs of pyloric obstruction 9 did well. One gained 137 ounces in sixty-one days. Excellent results were obtained by the administration of thick barley gruel in conjunction with breast-feedings by the method suggested by Current<sup>7</sup> for overnourished colic cases. One heaping teaspoonful of barley and a level teaspoonful of sugar were cooked down in 12 ounces of water to 8 ounces, and this was fed in small amounts before breast-feedings.

Durand concluded that thick cereal mixtures could safely be given in quantities of from 1 to 4 tablespoonfuls at a feeding, that such food was retained better than liquid, checked peristalsis and traversed the pylorus better than fluid in obstinate cases, and was to be employed before operation in pyloric cases. He considered the method serviceable in neurotic vomiting and certain types of malnutrition, and particularly effective in the treatment of colic in breast-fed infants.

The foregoing review suggests that the foundation has been laid for the application of concentrated cereal-milk feeding to a wide range of disorders, and to exemplify the results of such varied application the writer has selected records of 11 cases observed under different conditions. The babies treated under hospital supervision received the benefit of detailed study, but were not always supervised by the same physician or nurse, lacked the element of maternal care, and in spite of the usual safeguards were undoubtedly subject to moderate danger of infection.

#### CASE REPORTS.

CASE I.—*Mild Pylorospasm; Liquid Food Intolerance.* J. R. J., male, born at term, weighing 6 pounds, was nursed at three-hour intervals for seven weeks and then given a feeding of milk, water and dextrimaltose to supplement breast milk. When one month old he cried before feedings, vomited curds and showed evidence of colic, weighing only 5 pounds, 15 ounces. He was at first given

<sup>7</sup> Northwest Med., October, 1920, p. 240.

three two-ounce feedings daily of a mixture consisting of 2 ounces of whole milk, 4 ounces of water and 3 teaspoonfuls of dextrimaltose, to alternate with the nursings; but when seen one week later had developed forcible vomiting after almost every feeding and still weighed 5 pounds, 15 ounces.

He was then given a thick cereal feeding consisting of 10 ounces of milk containing 2 per cent fat, 10 ounces of water,  $3\frac{1}{2}$  tablespoonfuls of farina and 1 of cane sugar cooked down to 10 ounces. Two tablespoonfuls were given before the nursing of not to exceed ten minutes, five times daily, and  $2\frac{1}{2}$  tablespoonfuls were given without nursing twice daily. Only one vomiting attack occurred in the next four days and bowel movements to the number of two daily replaced the condition of constipation. During the next twenty days of thick cereal feeding supplementing breast milk in the manner described there was a gain of 1 pound. When, however the weight had reached 7 pounds vomiting recurred and gain in weight became slower, so that a change was made to a liquid formula consisting of 5 ounces of evaporated milk,  $2\frac{1}{2}$  tablespoonfuls of barley, 1 tablespoonful of sugar, water sufficient to make 25 ounces; 3 ounces without nursing three times daily,  $2\frac{1}{2}$  ounces with nursing four times daily. The vomiting immediately became worse and the weight fell to 6 pounds, 14 ounces in four days. A return was now made to the thick cereal feeding with the substitution of evaporated milk for the plain milk previously used: 5 ounces of evaporated milk, 3 tablespoonfuls of farina, 1 tablespoonful of cane sugar, water sufficient to make 20 ounces, the whole cooked down to 10 ounces, of which 1 to 2 tablespoonfuls were given at each feeding, nursing being permitted three or four times daily. The vomiting which had recurred on the liquid formula after nearly every feeding now ceased abruptly. Because, however, there was no appreciable gain in weight during the following ten days, although the evaporated milk portion in the formula had been increased to 6 ounces, nursing was discontinued.

A gain of  $\frac{1}{2}$  pound in the next eleven days followed, the stools which previously had shown the presence of starch became starch-free and vomiting ceased except after the administration of water or attempts to give orange juice.

The thick cereal feeding was maintained with gradual increase to include 7 ounces of evaporated milk,  $3\frac{1}{2}$  tablespoonfuls of farina,  $1\frac{1}{2}$  tablespoonfuls of sugar; and in spite of occasional vomiting the baby at four and a half months weighed nearly 9 pounds and was tolerating the cereal mixture to the amount of 65 calories per pound of body weight.

CASE II.—*Extreme Pylorospasm; Projectile Vomiting and Visible Peristalsis without Palpable Tumor.* L. D., female born of healthy parents at term, weighing  $6\frac{1}{2}$  pounds, was nursed for two weeks



and then given a feeding of 9 ounces of whole milk, 4 teaspoonfuls of "Imperial Granum" and 23 ounces of water;  $2\frac{1}{2}$  ounces every three hours. This was replaced by  $10\frac{1}{2}$  ounces of milk, 6 teaspoonfuls of dextrimaltose and 15 ounces of water; 3 ounces every three hours. At five weeks, vomiting, which had been occasional, became constant; obstinate constipation developed and loss of weight began to be rapid, so that on an initial examination at seven weeks she weighed only  $6\frac{1}{2}$  pounds.

Nutrition was extremely poor and during examination there was a sharp attack of projectile vomiting, accompanied by visible gastric peristalsis, which persisted in waves the size of an English walnut for some time after the stomach was emptied (although no pyloric tumor could be felt). A weak formula consisting of 8 tablespoonfuls of dry albumin milk (Hoos) in 24 ounces of water (3 ounces every three hours) was attempted, but 8 of 11 feedings during thirty-six hours were vomited and the weight fell abruptly to 6 pounds, 1 ounce.

At this point feeding of thick cereal and skimmed milk was begun: 24 ounces obtained after removal of top 8 ounces from quart bottle, 4 level tablespoonfuls of rice flour, 1 level tablespoonful of dextrimaltose, water to make 1 quart. This mixture was cooked down to 1 pint and fed from a spoon to the amount of  $2\frac{1}{2}$  tablespoonfuls every four hours. Practically all the food (350 to 400 calories) was greedily ingested in the twenty-four-hour period, and of the first 34 feedings only 3 were vomited. Normal movements occurred to the number of 2 daily and careful examination two days after the institution of the cereal feeding showed no starch in the stool. After five days a slight increase in the fat content of the mixture was attempted, but was withheld on the recurrence of projectile vomiting. The weight, however, had increased 10 ounces during the five days. During the succeeding week a reduced formula was maintained in the form of 20 ounces of milk (top 8 ounces removed), 4 tablespoonfuls of rice flour, 1 tablespoonful of dextrimaltose, water to make 30 ounces, the whole cooked down to 1 pint; and a special attempt was made to give  $\frac{1}{2}$  ounce of water three hours after the regular feedings. Four of 6 water feedings, however, were vomited while all but 5 of 33 cereal paste feedings were retained. The weight in five days on the reduced feeding fell to  $6\frac{1}{2}$  pounds, but in another five days, during which time  $2\frac{1}{2}$  tablespoonfuls at a feeding were given, rose to 6 pounds, 14 ounces.

Progress was here seriously interrupted by the recurrence of projectile vomiting following the administration of water. Vomiting subsided when the food was further reduced by a colleague to 18 ounces of fat-free milk, 4 tablespoonfuls of rice flour and 1 of dextrimaltose, with the added provision that the mixture should be peptonized. The weight, however, dropped rapidly to  $6\frac{1}{2}$  pounds, whereupon there were signs of circulatory failure.

The advisability of operation was now seriously considered, but in view of the quiescence of the vomiting a final attempt was made to increase the food intake and the following formula given: 6 ounces of evaporated milk, 4 tablespoonfuls of rice flour,  $1\frac{1}{2}$  tablespoonfuls of milk sugar, water to make 20 ounces. This was cooked down to 10 ounces and peptonized. Immediate improvement followed, and although no water was given during a period of two weeks the gain in weight was most gratifying: September 5,  $6\frac{1}{2}$  pounds; September 6,  $6\frac{3}{4}$  pounds; September 7, 7 pounds; September 12, 7 pounds, 7 ounces; September 26, 8 pounds, 3 ounces.

The cereal feedings with evaporated milk were gradually replaced during the fifth month by a liquid formula of evaporated milk, dextrimaltose and barley, at first given only once daily. Eventually the evaporated milk was replaced by ordinary milk, and at the age of thirty-six weeks the baby weighed  $16\frac{3}{4}$  pounds, and was apparently normal.

The administration of atropin sulphate was begun early in this case and continued, for several weeks in dosage gradually increased from  $\frac{1}{1000}$  gr. to  $\frac{1}{200}$  gr. every four hours. No undue effects were noted and probably a much larger dose might have been employed, as recommended by Haas,<sup>8</sup> had the vomiting not been controlled.

**Summary.** Obstinate pylorospasm in a female infant of seven weeks was successfully relieved by the administration of concentrated skimmed milk-cereal and evaporated milk-cereal mixtures after the withholding of all liquid. Starch digestion appeared to be complete. Peptonization and the administration of moderate doses of atropin were employed, but did not appear determining factors. Gain in weight was maintained on the giving of a mixture supplying 70 calories per pound, while rapid loss occurred even when vomiting was under control, on limitation of this allowance to 55 calories.

**CASE III.—*Extreme Pylorospasm; Projectile Vomiting; Visible Peristalsis and Palpable Tumor; Stenosis Incomplete.*** S. C., male, born at term, was brought under dispensary observation when five weeks old, weighing 8 pounds, 11 ounces. He was unusually hungry, constipated and occasionally vomited, but in other respects conformed to normal. The attempt to feed in small amounts alternately with the nursing a mixture of 16 ounces each of whole milk and water containing a tablespoonful of "Imperial Granum" was followed by more frequent vomiting, which persisted after both nursing and bottle-feeding, when the supplementary formula was changed to 3 ounces of whole milk, 6 ounces of water and 3 teaspoonfuls of cane sugar, 3 ounces three times daily. At the end of a month the weight had fallen to 8 pounds, 2 ounces, and

<sup>8</sup> Arch. Pediat., September-October, 1919.

although a gain of 7 ounces in ten days was then obtained on feedings of 3 tablespoonfuls of dry milk powder and 1 teaspoonful of dextrimaltose in 4 ounces of water, the vomiting increased, and when the infant was thirteen weeks old became actually projectile. The weight in consequence fell to 8 pounds in five days.

At this juncture the baby was admitted to the hospital with the record (by an experienced observer) of a visible peristaltic wave and a palpable tumor at the site of the pylorus.

Cereal-milk feeding was administered in the form of a mixture of 14 ounces of whole milk, 5 tablespoonfuls of farina and 1 of sugar, cooked down with water to a thick paste, of which 5 tablespoonfuls were given as the only food six times daily. Vomiting at once subsided and roentgen-ray examinations and aspirations of gastric contents alike failed to reveal abnormal food retention. Under later dispensary supervision feeding of the same type was continued until at the expiration of eight weeks a weight of  $11\frac{1}{2}$  pounds was attained. Unfortunately progress was then interrupted by a severe cold accompanied by diarrhea and fever rising at one time to  $105^{\circ}$ , necessitating a second period of hospital care. Protein milk in liquid form was well tolerated during this attack, and upon its termination a milk, sugar and barley modification in the usual liquid form was given. This was maintained, with excellent results, until the latter part of the first year, at which time development was practically normal.

The existence for even a brief period of a palpable pyloric tumor in a case which nevertheless responded so promptly to the thick cereal must be regarded as exceptional, and by no means as an argument against operation in the presence of similar signs, with more persistent obstruction.

CASE IV.—*Complete Pyloric Stenosis with Palpable Tumor; Operation; Recovery.* E. Q., male, was admitted to Bellevue Hospital at the age of four weeks weighing only  $6\frac{1}{2}$  pounds, despite the record of a birth weight of 9 pounds. He had been breast-fed, but in the two weeks prior to admission was reported to have lost 2 pounds, owing to projectile vomiting, which began at two weeks. He had always been constipated. Upon examination he appeared wrinkled and pale and was found to have a small tumor in the right hypochondrium about half the size of a peanut. An attempt was made to administer a thick cereal paste consisting of  $7\frac{1}{2}$  ounces of whole milk,  $7\frac{1}{2}$  ounces of water, 3 tablespoonfuls of farina and 1 of cane sugar, cooked down to solid consistency. This was retained during the first eighteen hours, then violently vomited *en masse*.

The patient was immediately hurried to operation, which was performed twenty-four hours after admission to the hospital. The stomach was greatly dilated, and the pylorus, measuring 1 by 2

cm., was discovered to be as hard as cartilage and much hypertrophied. An incision 2 cm. long was made through the muscular coats down to the mucosa, after which the wound was closed in the ordinary manner. The baby then did well on breast-milk feedings, showing no recurrence of the vomiting, and making a continuous and uneventful recovery and gain.

This case shows the limitations of even the thick cereal feeding in dealing with true pyloric stenosis, and is presented with the frank purpose of offsetting any inclination on the part of the physician to employ any feeding method too persistently in instances in which the underlying condition is beyond doubt surgical rather than medical.

CASE V.—*Persistent Projectile Vomiting at Fourteen Months; Delayed Growth.* F. F., male, born supposedly at term, weighed only 5 pounds. He was nursed for nine months, receiving supplementary modified milk-feeding after five months. Vomiting occurred first at two weeks. It was reported to have been projectile and persisted up to the age of fourteen months, when the baby was referred for treatment, weighing  $14\frac{1}{4}$  pounds. Constipation had been constant from the beginning of cows' milk feeding. Although liquid milk was consistently vomited, certain solid food articles, such as zwieback, potato and dry milk powder, without water, were greedily taken and often retained. Physical examination revealed no abnormalities and no evidences of rickets. The child was uniformly small and of an infantile type.

An attempt to feed a weak liquid evaporated milk formula prepared with rice flour and dextrimaltose was unsuccessful and a thick cereal feeding was substituted, containing 4 tablespoonfuls of rice flour and 2 tablespoonfuls of dextrimaltose, with 28 ounces of milk and 4 of water, the entire mixture being cooked down to 18 ounces. This was supplemented by plain cereal, broth thickened with gruel, junket, bread, butter and potato.

The vomiting persisted, but at intervals of greater and greater length, and gradually took on less severity, so that much of the stomach contents was not expelled. The weight, however, fell during the first nineteen days to 13 pounds, and did not again reach  $14\frac{1}{4}$  until two months from the time the patient was first seen. Vomiting even then occurred, although improvement in the general condition was apparent. During the eighteenth month unmodified milk-feeding was instituted and the diet was enlarged to include vegetables and bread and butter more liberally.

At two and a quarter years the patient was in good health, without evidence of rickets, weighing  $19\frac{1}{2}$  pounds. He still belonged to a type bordering on the infantile, but promised to outgrow this classification.

CASE VI.—*Liquid Food Intolerance at Three Months.* M. M., female, weighing  $7\frac{1}{2}$  pounds at birth, began to vomit at two months after nursing at intervals of two and half hours. Vomiting had increased on a formula composed of 10 ounces of whole milk, 1 tablespoonful of barley, 4 teaspoonfuls of milk sugar,  $4\frac{1}{2}$  ounces every two and a half hours, and had not been lessened by the substitution of 6 ounces of evaporated milk for the whole milk. When examined at the age of three months the baby weighed  $8\frac{1}{4}$  pounds, was pale, poorly nourished and looked ill. Gastric lavage two hours after the feeding brought up only a small amount of mucus.

A feeding consisting of 8 to 10 ounces of 2 per cent milk, 3 tablespoonfuls of farina and 1 of sugar, with sufficient water to make 26 ounces, was cooked down to half its volume and the resulting thick paste was fed to the amount of 2 to  $2\frac{1}{2}$  tablespoonfuls every three hours.

Five days later, as there was only occasional regurgitation and the baby seemed very hungry, the formula was increased to include 10 ounces of whole milk,  $3\frac{1}{2}$  tablespoonfuls of farina and  $1\frac{1}{3}$  tablespoonfuls of sugar; 3 tablespoonfuls being given every three hours. The weight increased during a period of eleven days from  $8\frac{1}{4}$  to  $8\frac{1}{2}$  pounds, but the occurrence of green stools with much gas upon attempt at further increase in the food necessitated a return to the first cereal formula. Meanwhile, inaccuracy in the home record made it impossible to compute the exact twenty-four hours' intake. At the end of eleven days of the cereal feeding the use of evaporated milk in place of the ordinary milk was begun with a formula containing 8 ounces of evaporated milk,  $3\frac{1}{2}$  level tablespoonfuls of farina and 1 tablespoonful of sugar, cooked down with water to 8 ounces and fed in amount up to 3 tablespoonfuls every three hours. The mother was conservative and reduced the milk to 6 ounces. This may have accounted for the slight gain of only 3 ounces in the ensuing twelve days. From this point on, however, a larger quantity of food was prepared, and although it was expected that all would not be used, the following formula (through misunderstanding) was given in its entirety every twenty-four hours: 14 ounces of evaporated milk,  $5\frac{1}{2}$  tablespoonfuls of farina,  $2\frac{1}{2}$  tablespoonfuls of sugar, water to make 1 quart, the whole cooked down to 15 ounces, supplying nearly 90 calories per pound of body weight. The effect was immediate. Vomiting ceased, the stools became uniformly good and a gain of 18 ounces occurred in six days. Meanwhile an attempt to feed one bottle of dry milk powder dissolved in water occasioned vomiting and hiccough. The cereal formula was accordingly maintained with slight reduction, and at the expiration of another three weeks the weight had increased to 11 pounds, 9 ounces, making the total gain for twenty-seven days on the high calory formula 45 ounces.

Progress continued on the thick cereal combined with evaporated

milk and supplemented by the administration of orange juice, until at seven months the baby weighed  $15\frac{3}{4}$  pounds. The gain during the final ninety-four days, in spite of the occurrence of chicken-pox, was 97 ounces.

CASE VII.—*Breast-milk Idiosyncrasy Intolerance of Liquid.* R. K., female, was born at term, weighing 7 pounds. During pregnancy the mother had had marked symptoms of toxemia, but at the time of labor was in fair condition. The baby began to vomit at the very outset and continued vomiting after practically every nursing. At the end of one week, during which breast milk only was given, vomiting was accompanied by an attack of choking and cyanosis, which caused great alarm, and apparently might readily have culminated in suffocation. Similar attacks of less severity had previously occurred. Upon examination the infant appeared normal, weighing 7 pounds and presenting no evidence of pyloric tumor or intense gastric spasm. Lavage obtained a moderate amount of mucus but very little food residue. The stools were fairly normal.

Nursing was suspended for a period of twelve hours, during which a mixture consisting of 3 tablespoonfuls of farina and 1 of cane sugar in 1 pint of water, cooked down to 8 ounces, was fed at three-hour intervals with a spoon. After twelve hours 3 ounces of whole milk were incorporated in the formula. All of the cereal feedings were eagerly taken and retained. At the end of this period a nursing was retained, but repetition of nursing after another twelve hours occasioned vomiting. During the second week of life the formula was increased to include 6 ounces of milk, with no unfavorable result. After five days of this procedure nursing was again attempted for three minutes only at every second cereal-feeding, but slight vomiting recurred, and at about the end of the second week there was another serious choking attack. At this time an ordinary skin test was made with a drop of the mother's milk. An urticarial wheal, livid, elevated and of about the diameter of a dime, became apparent in about five minutes and faded slowly, indicating that the infant was possibly sensitized against the breast milk. Nursing was still permitted with caution at the mother's request, but by the end of the third week had been found absolutely futile, while even the administration of water caused discomfort and occasional vomiting.

Cereal-feeding was successfully maintained, with further increase in the formula, until by the end of the fourth week a mixture incorporating 9 ounces of whole milk,  $3\frac{1}{2}$  tablespoonfuls of farina and  $1\frac{1}{2}$  tablespoonfuls of cane sugar was being taken. This was followed, with little modification until the end of the fifth month, at which time the baby weighed  $13\frac{1}{2}$  pounds.

This case illustrates the fact that intolerance of breast milk may

exceptionally constitute a very definite clinical entity analogous to other forms of allergy and demonstrates, furthermore, the possibility of successfully administering thick cereal during the earliest weeks of life if liquid food is not tolerated.

Subcutaneous injection of breast milk as a means of desensitization in similar instances of intolerance by nurslings has recently been reported to have given excellent results.<sup>9</sup>

CASE VIII.—*Breast-milk Colic.* L. H., female, was the fifth child of healthy parents, born at term, weighing  $7\frac{1}{2}$  pounds. After nursing for one month she developed marked colic, accompanied by occasional vomiting and green stools to the number of three daily. At one month her weight was 7 pounds, 3 ounces. She was given a mixture of 6 ounces of 2 per cent milk, 6 ounces of water, 3 tablespoonfuls of farina and 1 tablespoonful of cane sugar, cooked down to a thick paste, of which 1 tablespoonful was fed regularly before nursing. The food was well taken and the colic abated, the stools becoming more solid and of better appearance, although showing much starch. The weight in sixteen days increased 14 ounces. During this period an attempt was made to feed 2 tablespoonfuls of dry milk powder in 2 ounces of water occasionally in place of the cereal. Vomiting, however, resulted and the mother reported that when the cereal feeding was omitted nursing seemed to cause discomfort.

From this time the case was followed only irregularly, but by the end of the third month, despite some improvement in the mother's nursing capacity, the cereal feedings had been proved to agree better than exclusive nursing or conservative feeding of dry milk in water. The weight had increased to 10 pounds, and although the infant was still undernourished and pale, she was becoming muscularly stronger and gave promise.

CASE IX.—*Acute Ileocolitis with projectile Vomiting.* R. M., female, with negative family history, weighing  $7\frac{1}{2}$  pounds at birth, was bottle-fed from the outset under milk-station supervision. She had vomited a small portion of every feeding after the sixth day of life, but the vomiting had not been projectile. Diarrhea to the degree of three or four loose green stools daily had accompanied the vomiting. Loss of weight had been progressive.

She was admitted to Bellevue Hospital at the age of six and a half weeks, weighing 4 pounds, 15 ounces. She was pale, emaciated, dehydrated, with sunken fontanel and soft scaphoid abdomen. Leukocytes numbered 20,000; polynuclears, 88 per cent; lymphocytes, 12 per cent. Von Pirquet test was negative. The tempera-

<sup>9</sup> Weil: Jour. des praticiens, September 20, 1920, and Médecine, August, 1920. Starek: Anaphylaxis to Breast Milk, Archives de médecine des enfants, Paris, September, 1921.

ture, 96° at noon, on admission, rose to 106.5° at 8 P.M., following an intraperitoneal injection of 75 cc of saline, then fell to normal.

During three days liquid feedings were attempted in the form of barley water alone, boiled protein milk and barley water, whey and albumen water and whey alone. The food was well taken but immediately vomited. Twenty instances of vomiting were noted in the first three days and only two of retention. On the third day the vomiting occurred nine times, and saline intraperitoneally was again employed. Meantime the stools, though liquid and green, had slightly improved. The weight had been increased, probably by the saline, to 5 pounds, 2 ounces.

At this point the feeding of thick cereal was begun with a mixture prepared by cooking together 5 ounces of whole milk, 5 ounces of water and 2 tablespoonfuls of farina. Vomiting immediately ceased and the stools became yellow and pasty. Two days later the mixture was increased to include 8 ounces of milk, 3 tablespoonfuls of farina and 1 tablespoonful of cane sugar. No vomiting whatever occurred in a period of three days, at the expiration of which time the weight had increased 3 ounces. Liquid food was again offered three times in a period of two days in the form of 1 ounce of whole milk, 2 ounces of barley water and  $\frac{1}{2}$  teaspoonful of sugar, but the occurrence of projectile vomiting compelled discontinuance. The weight remained stationary for about a week. Then the cereal mixture was increased to 9 ounces of whole milk, 3 tablespoonfuls of farina and  $\frac{3}{4}$  tablespoonful of sugar,  $2\frac{1}{2}$  tablespoonfuls being given every three hours. No food was left and no vomiting occurred. The stools were yellow, of normal consistency, and showed no starch. Improvement was further manifested by the gain of 5 ounces in 8 days. Even at this time, in spite of the fact that the giving of small amounts of orange juice had been successful, one bottle-feeding daily of modified milk and barley water occasioned vomiting.

Further progress was prevented by the development of pyuria accompanied by a rise in temperature. Ultimately the patient died of erysipelas exactly two months after admission to the hospital.

Cereal feeding had been maintained throughout the case without apparent untoward effects.

#### CASES X AND XI.—*Prematurity with Defective Assimilation.*

CASE X.—S. S., female, was the offspring of a mother who during her pregnancy had active syphilis and received six treatments with salvarsan, the latter treatments being conducted within one month of the birth of the child. The baby was born at term, weighing 5 pounds, 3 ounces, showing no evidence of syphilis, but gonorrheal ophthalmia on the first day of life.

She was fed for eight days on a whole milk, lactose and barley



formula supplying about 50 calories per pound of body weight and of the approximate percentage composition: fat 2, sugar 5 and protein 1.5. During the eight days her digestive symptoms were fairly good, but her weight fell to 4 pounds, 15 ounces. She was then gradually introduced to a formula of 1 to  $1\frac{1}{2}$  tablespoonfuls of dry milk with 1 teaspoonful of cane sugar in  $2\frac{1}{2}$  ounces of water, breast milk being substituted occasionally when this was available. Her weight fell to 4 pounds, 13 ounces, and attempts to increase the food were frustrated by an increasing tendency to diarrhea. She was then given a formula of evaporated milk, dextrimaltose and barley water, supplying 55 to 65 calories per pound. The stools improved and she became actually constipated, but the weight fell to  $4\frac{1}{2}$  pounds, so that at five weeks she weighed 11 ounces less than at birth.

At this point a mixture consisting of  $7\frac{1}{2}$  ounces of whole milk,  $7\frac{1}{2}$  ounces of water, 3 tablespoonfuls of farina and 2 tablespoonfuls of cane sugar, cooked down to a thick paste, was introduced. The baby appeared satisfied; the stools were soft and yellow, although containing starch; and the weight increased  $6\frac{1}{2}$  ounces in six days.

Nevertheless, the infant suddenly became apathetic, then stuporous and died before the determination of any definite acute disease could be made. Although no autopsy was obtained it seems probable that the fatal outcome was induced by congenital syphilis.

CASE XI.—E. L., female, with negative family history, was born prematurely in the obstetrical ward of Bellevue Hospital, weighing 4 pounds. Except for the lack of development she appeared normal. She was fed on breast milk supplemented by boiled milk and water for two weeks and then admitted to the premature ward, weighing 3 pounds, 11 ounces. Under modified whole-milk feeding, replaced after about a week by a combination of 4 ounces of 6 per cent milk, 2 drams of lactose and 12 ounces of whey; 2 ounces at each of eight feedings (200 calories daily), the weight increased to 4 pounds, 2 ounces in a period of two weeks, then remained stationary, and on the occurrence of green stools, when the infant was five weeks old, fell to 3 pounds, 15 ounces. A mixture was then introduced consisting of  $7\frac{1}{2}$  ounces of 1 per cent milk,  $7\frac{1}{2}$  ounces of water, 3 tablespoonfuls of farina, 2 drams of sugar, the whole cooked down to a paste supplying 280 calories and fed with a spoon at two-hour intervals. The stools immediately became yellow and pasty, showing, however, the presence of undigested starch, and the weight increased at the rate of nearly an ounce daily to 4 pounds, 6 ounces. The gain was at this point interrupted, although there was no apparent digestive disturbance, and at the end of eighteen days' trial a liquid formula incorporating less farina was instituted: whole milk 9 ounces, farina 1 tablespoonful, cane sugar  $\frac{3}{4}$  ounce, water to complete 21 ounces (300 calories), 3 ounces at seven feedings. This was well tolerated and the weight increased 11 ounces

in a period of fifteen days. Gain was then again deferred and after a few days a discharge of pus occurred from the right ear simultaneously with the development of conjunctivitis. Nutrition was maintained on liquid feeding during the succeeding month, with some degree of improvement after the first two weeks, the weight finally reaching  $5\frac{3}{4}$  pounds. At this point, however, the infant became rapidly worse, apparently from general sepsis, and died at sixteen weeks.

This case illustrates a satisfactory temporary gain on thick cereal feeding given over a period of eighteen days to a premature infant, one month old, weighing only 4 pounds.

**Conclusions.** From so brief a series of cases positive deductions are not to be drawn. The observations recorded, however, correspond closely with those of previous observers and reinforce the claim that thick cereal is of exceptional value in controlling vomiting dependent on pylorospasm. The use of similar feedings in conjunction with nursing may likewise have a desirable antispasmodic action on both stomach and intestine. Applicability of the thick cereal method to certain acute forms of diarrhea, which are not favorably affected by the usual protein milk regimen, may later be established. The improvement at a very critical stage manifested in the case of ileocolitis with projectile vomiting is not without significance, while tolerance for the thick cereal exhibited by two premature infants who had assimilated liquid food poorly is worthy of special emphasis, notwithstanding the fatal outcome induced by infection.

While better results are to be obtained in the home than in the hospital, exceptions to this rule are obvious. In a dispensary case of apparent simple pylorospasm a period of forty-eight hours between visits was sufficient for the development of complete stenosis and the failure of an operation which otherwise might have been timely and successful. In such a situation twelve to twenty-four hours will ordinarily suffice to show whether continued administration of the thick cereal is justifiable, and if, throughout this period, improvement is lacking, immediate operation by the Fredet-Rammstedt method, so successfully adapted by Downes,<sup>10</sup> is to be looked upon as conservative.

In this connection one should nevertheless remember that a paradoxically-behaving pylorus which permits the passage of semisolid, but not liquid, food may invite an error in diagnosis even when the roentgen-ray is employed.

The cereal of choice is probably farina, because of its property of great expansion under cooking, thus permitting thickening of the mixture with a minimum amount of added starch. Three or

<sup>10</sup> Jour. Am. Med. Assn., June 27, 1914. Surg., Gynec. and Obst., March, 1916.

4 tablespoonfuls in a 20-ounce formula will ensure sufficient solidification by the time cooking has reduced the quantity one-third, although greater concentration may at times be advisable. Obviously the amount of water to be used is not arbitrary. Skimmed milk, evaporated milk, dry milk powder or breast milk may be incorporated in preference to whole milk. Sugar of any form may be employed, but should be maintained at a low percentage until tolerance is proved, with due regard for the possible ill effect of maltose when vomiting is a chief symptom. For an infant under six months of age an allowance of 2 or 3 tablespoonfuls at a feeding ordinarily suffices. If more is demanded the indication is for a thicker rather than a larger feeding.

The calory guide is more valuable than the percentage method in calculating the ration. Empirically it has been found that 60 to 75 calories per pound of body weight may be required to maintain a satisfactory gain, and that a larger allowance may be demanded and tolerated.

The importance of starch-free stools is likely to be magnified. Complete starch digestion is, of course, advantageous, but if incomplete digestion of the starch gives rise to no concomitant colic, distention or hiccough the method may be continued with appreciation that the cereal is at least serving as a good vehicle.

Water between feedings is desirable, but not at all times necessary. In Cases II and VI none was given apart from the almost solid feedings for as long as two weeks, and in neither instance were there evidences of dehydration or thirst.

The writer acknowledges helpful courtesies from fellow-members of the children's medical division of Bellevue Hospital.

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## SPLENIC AND HEPATIC ENLARGEMENT IN ENDOCARDITIS: A STUDY OF TWO HUNDRED AND EIGHTY-SIX AUTOPSY FINDINGS.

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**I. Introduction.** Although much has been said and written upon the subject of subacute endocarditis, yet this condition is still frequently overlooked. Since splenic enlargement is an important diagnostic sign in endocarditis, which has as yet hardly received sufficient emphasis, it was felt that more information regarding its occurrence should be gathered. Accordingly, from the records of the University Hospital and the autopsy protocols of the department of pathology in the medical school of the University of Penn-

sylvania such a study was made, the spleens of acute and recurring endocarditis being compared with those of chronic cardiac disease on the one hand and non-cardiac streptococcic infections on the other; the frequency and degree of hepatic enlargement were also noted.

Indebtedness is here gratefully acknowledged to Dr. Alfred Stengel, at whose suggestion this study was undertaken, and to Dr. Allen J. Smith, of the pathological department, whose records form the basis of this report.

**II. Technic.** Autopsy findings upon infants and small children were omitted from consideration since the relatively smaller number of children examined post mortem by the department of pathology would confuse the results from the statistical standpoint. Where the weight of organs was not stated in the protocols this was calculated from the size. In the autopsy records some organs were reported as "normal in size," "enlarged" or "greatly enlarged." In the tables which follow, such data is used in calculating the frequency of enlargement but omitted where *degree* of enlargement is under consideration. Where no mention whatever was made of the size of organs the case was omitted from consideration, as were also all cases in which there occurred some other condition commonly producing splenic enlargement, as, for example, malaria, typhoid fever or leukemia.

Vierordt's tables furnished the basis for estimating the average weights of the liver and spleen for each decade of age.

The question of how much an organ might deviate from the average in weight before it should be regarded as pathologically enlarged was decided upon after studying the variation from normal of a series of spleens in which no condition existed at autopsy which might be supposed to cause enlargement. Fifty per cent increase was regarded as showing undue enlargement of the spleen and 30 per cent undue enlargement of the liver.

No attempt was made to separate cardiac cases into any but three general groups: (1) Those with evidences of an acute process only; these are referred to as "recent acute endocarditis." (2) Those with evidences of a chronic process only; these are referred to as "chronic cardiac disease." (3) Those with evidences of a chronic process and an acute process in addition; these are referred to as "recurring endocarditis." Probably both groups (1) and (3) contain cases of so-called subacute infectious endocarditis or *Streptococcus viridans* infection; but because of the difficulty of diagnosing this condition from autopsy reports, often without clinical histories or blood cultures, no attempt was made to group these cases separately.

The group of non-cardiac streptococcic infections was gathered from the autopsy protocols of the Pennsylvania Hospital, the Philadelphia General Hospital and the University Hospital, and

comprises only those cases in which a culture revealed streptococci apparently as the cause of death and where the endocardium was apparently normal.

### III. Findings.

TABLE I.—FREQUENCY AND DEGREE OF SPLENIC AND HEPATIC ENLARGEMENT.

Diagnosis.	Spleen.				Liver.		
	Number cases.	Number enlarged.	Percent-age enlarged.	Degree of enlargement, <sup>2</sup> per cent.	Number enlarged.	Percent-age enlarged.	Degree of enlargement, <sup>2</sup> per cent.
Recent acute endocarditis . .	57 <sup>1</sup>	29	50	241	14	25	69
Recurring endocarditis . .	88	45	51	236	26	30	58
Chronic cardiac disease . .	87	20	23	146	15	17	40
Non-cardiac streptococcic infections . .	54	24	44	129	17	31	55
Total . .	286	118			72		

<sup>1</sup> Fractions are omitted, the nearest integer being used.

<sup>2</sup> Under this head are included only organs whose numerical weight or size was given.

If the enlarged spleen of endocarditis is due to back pressure alone it would seem reasonable to expect a greater enlargement to occur in chronic cardiac disease than in acute or recurring endocarditis. This is not the case. Furthermore, splenic enlargement is more frequent and more marked in non-cardiac streptococcic infections than in chronic cardiac disease. This speaks for the correctness of the commonly held belief that in acute and recurrent endocarditis the splenic enlargement is in great measure dependent upon infection.

TABLE II.—RELATIONSHIP OF SPLENIC INFARCTION AND ENLARGEMENT

Diagnosis.	Number cases.	Infarcts.	Percent-age having in-farcts.	Infarcts without enlarge-ment.	Infarcts with enlarge-ment.	Percent-age of enlarged spleens infarcted.	Percent-age of infarcted spleens enlarged.
Recent acute endocarditis . .	57	21	37	7	14	48	67
Recurring endocarditis . .	88	23	26	8	15	33	65
Chronic cardiac disease . .	87	8	9	6	2	10	25
Non-cardiac streptococcic infections . .	54	3	6	1	2	5	77

TABLE III.—RELATIONSHIP OF AGE TO SPLENIC ENLARGEMENT.

Diagnosis.	Below 20	20-30	30-40	40-50	50-60	60-70	Above 70	No age given	Total or average.
Recent acute endocarditis . . .									
	Number of cases . . . . .	1	14	8	14	5	4	7	57
	Number enlarged . . . . .	0	6	6	6	5	0	4	29
	Percentage enlarged . . . . .	0	43	75	43	100	0	57	50
	Degree of enlargement . . . . .	0%	231%	369%	134%	248%	0%	131%	241%
Recurring endocarditis . . . .									
	Number of cases . . . . .	4	7	15	18	11	4	18	88
	Number enlarged . . . . .	2	2	12	12	4	1	8	45
	Percentage enlarged . . . . .	50	28	80	67	36	25	44	51
	Degree of enlargement . . . . .	220%	215%	299%	248%	177%	80%	251%	236%
Chronic cardiac disease . . . .									
	Number of cases . . . . .	4	11	29	11	7	7	7	87
	Number enlarged . . . . .	0	2	5	3	1	2	3	20
	Percentage enlarged . . . . .	0	18	17	27	14	29	43	23
	Degree of enlargement . . . . .	0%	64%	288%	106%	195%	55%	89%	146%
Non-cardiac streptococcic infections									
	Number of cases . . . . .	2	8	8	6	7	4	15	54
	Number enlarged . . . . .	1	2	0	3	4	2	8	24
	Percentage enlarged . . . . .	50	25	0	50	57	50	53	44
	Degree of enlargement . . . . .	not stated	64%	0%	159%	167%	125%	161%	129%

From these figures it could not be well argued that infarction was the usual cause of the splenic enlargement, for in less than half of the cases in which splenic enlargement occurred was infarction found. As might be expected, however, many of those with infarcts showed splenic enlargement.

Splenic enlargement is found to be considerably less frequent and less marked in cardiac cases over seventy years of age than in younger individuals. Other than this no relationship between age and splenic enlargement appears to exist.

In comparing autopsy findings with hospital records in 30 University Hospital cases it was found that frequently (in 32 per cent) the livers were expected to be found enlarged but did not appear so at autopsy, while in 20 per cent the spleens were not suspected but were found at autopsy to be enlarged.

**IV. Conclusions.** The spleen was often found greatly enlarged in patients who had died of acute or recurring endocarditis, and this enlargement occurred independently of liver enlargement. Splenic enlargement was also frequently found in cases with non-cardiac streptococcic infection and about half as frequently in chronic cardiac disease. Although it is impossible to arrive at any final conclusion as to the cause of splenic enlargement in acute and recurring endocarditis, the evidence points toward infection rather than back pressure or infarction as being the factor of most importance in causing the spleen to enlarge. Splenic enlargement is an important diagnostic sign in acute and recurring endocarditis, and is frequently overlooked in the physical examination.

## REVIEWS.

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ESSENTIALS OF HISTOLOGY. By SIR EDWARD S. SCHAFER, F.R.S., Professor of Physiology, University of Edinburgh. Eleventh edition. Pp. 577; 720 illustrations. Philadelphia and New York: Lea & Febiger, 1920.

THIS volume is intermediate in size between the author's *Text-book of Microscopic Anatomy* and his smaller *Course of Practical Histology*, and its contents are well indicated by its title. The first edition of this standard work was issued in 1885, when it contained 245 pages and 281 figures. A glance at the first edition shows that already at that time the foundations of histology had been well laid. Many of the figures of Ranvier, Klein and Recklinghausen, which are shown there, are still used in the last edition, and some of the unsolved problems of those days have not yet been completely answered. Thus, the same description is given of the capillaries of the bone marrow: "Indeed, according to some authorities, the walls of the capillaries are imperfect, so that there is an open communication between them and the interstices of the tissues." This is still a moot point. The organs to which more space is now devoted are the endocrine glands. The hypophysis and parathyroids were not included in the first edition, and scant attention was paid to the adrenal. In the succeeding editions new matter and new illustrations have been added continually to keep the presentation abreast of the times. The book is now printed on thin paper, is of convenient size and has many colored illustrations. These, in many cases, show examples both human and from other mammals, but in the figures of mammary gland only the conditions seen in the cat are shown. It is with surprise that one notices the thickness of the cementum shown extending up to the neck of the tooth. It must be seldom that such a condition is met with in the normal tooth. An important part of the book has always been the directions for practical work, and in the appendix is given a selection of useful methods.

W. H. F. A.

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SYPHILIS AND ITS TREATMENT. By WINFRID S. FOX, M.A., M.D., St. George's Hospital, London. First edition. Pp. 185; 53 illustrations (22 in color). New York: Paul B. Hoeber, 1921.

A BRIEF treatise of 185 pages, devoted to a most intelligent and judicious exposition of this disease as it is most frequently



encountered. The author omits the burdensome chapters on how syphilis manifests itself in the various systems and organs, and limits the description to the disease as though seen in the active outpatient department. There are very few references in the book and the reader is carried along as though listening to the lecture of one intensely interested in his subject and patients. The style is excellent, the illustrations well chosen, and his conclusions, especially in interpreting the Wassermann test and the choice of methods of treatment, seem lucid and based on close observation and analysis of vast personal experience. One misses the exposition of the disease as encountered in the negro, where its cutaneous manifestations take on peculiarities and its diagnosis and course show racial differences. We would also criticize the use of the words "split-pea" and "three-penny-piece" as being too vague and non-scientific. The statement that hemiplegia is "the commonest nervous disorder seen in the course of the disease" is also open to question. It is a pity to point out these—the only faults noted—as criticisms of a book whose worth otherwise is far above the average; and we take pleasure in recommending it to the general practitioner who wants a guide in therapy and an exposition of the symptoms and signs of this ever-present disease.

A. R.

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THE SPHYGMOMETER. By WILLIAM RUSSELL, M.D., LL.D., Ex-President, Royal College of Physicians, Edinburgh; Professor-Emeritus of Clinical Medicine, Edinburgh University; Consulting Physician, Royal Infirmary, Edinburgh. Pp. 145; 14 illustrations. New York: William Wood & Co., 1921.

THE author believes that physicians are misled in placing their faith upon sphygmometer readings as indicating the pressure of the blood within the arteries. He believes that in cases of so-called hypertension vascular spasm is frequently present resulting in narrowing of the lumen and thickening of the arterial wall. These changes, he believes, result in an actual diminution of pressure within the artery and a false elevation of sphygmometer readings.

The book consists largely of lectures delivered between 1908 and 1916 in which case histories are discussed, with a brief reference to physical findings and treatment, and considerable repetition of the author's views regarding vascular spasm.

The literature upon this subject is largely ignored by the author, but he refers briefly to four observations of his own upon excised arteries. These, as well as his more numerous clinical observations, are by no means convincing.

J. H. A.

A TEXT-BOOK OF BIOLOGY. By WILLIAM MARTIN SMALLWOOD, PH.D., Professor of Comparative Anatomy, Syracuse University. Fourth edition. Pp. 308; 229 illustrations and 3 plates in color. Philadelphia and New York: Lea & Febiger, 1920.

IN the fourth edition of this college biology, new chapters have been added and others enlarged, but in general the same plan of arrangement has been followed as in the preceding edition. It is a very readable book, full of interesting facts about plants and animals, and is to be used for supplementary reading in conjunction with the laboratory work in first-year college courses in zoölogy and botany.

W. H. F. A.

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TEXT-BOOK OF NERVOUS DISEASES. FOR the Use of Students and Practitioners of Medicine. By CHARLES L. DANA, A.M., M.D., LL.D., Professor of Nervous Diseases, Cornell Medical College. Ninth edition. Pp. 624; 262 illustrations and 4 color plates. New York: William Wood & Co., 1920.

THE ninth edition of Dr. Dana's text-book differs from its predecessors mainly by the incorporation in this volume of a new and comprehensive chapter on "medical psychology" and a rather brief chapter on "endemic encephalitis or encephalitis lethargica." The remainder of the book is practically a reprint of the eighth edition of 1915 with the exception that there is a general elaboration of the chapter on the diseases of the peripheral nerves by material gleaned from the teachings of the war, especially as regards neurological surgery and injuries to the nerves. The section dealing with the psychoneuroses has also been somewhat altered as a consequence of the teachings of war experience.

Little space is given to endocrinology because, as the author states, "Endocrinology is still an elusive science and is not yet a body of classified knowledge—and belongs broadly to internal medicine."

The new chapter on psychology, in its dynamic, descriptive and physiological phases, emphasizes those fundamental things which every student ought to know in order to reason clearly on the subject. This chapter is manifestly antagonistic to psycho-analysis as a new science. In it the author endeavors to counteract the present-day tendency to mysticism and symbolism by portraying a normal and rational interpretation of dynamic psychology. Dr. Dana whimsically states, "As showing a present somewhat hypomanic trend, more than twenty books have been recently published on psycho-analysis, about one-fifth being by lay writers, and all may be found in a general bookstore on counters much patronized by women."

The ninth edition of Dana's text-book continues to hold its place of eminence as one of the standard works on neurology for students and practitioners.

F. H. L.

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FUNCTIONAL NERVE DISEASE. An Epitome of War Experience for the Practitioner. Edited by H. CRICHTON MILLER, 'M.A., M.D., Late Consulting Neurologist, Fourth London General Hospital. Pp. 198. London: Oxford University Press, 1920.

THIS rather unusual book is divided into twelve chapters, each chapter being written as a separate entity by a different author. The several writers are not in entire agreement with one another, hence conflicting views are expressed which tend to confuse the reader.

There are four main divisions to the book. The first of these divisions is entitled "The Physical Factor" and contains chapters by Crichton Miller, M.D., George Riddock, M.D. and Dr. Edwin Bromwell, all of which are written in an easy readable style and the opinions expressed are very logical. The second deals with the "Hysterical Factor" and is in four chapters. Dr. E. Prideaux has dealt with the "Mechanism of Hysteria" in a way which is not wholly Freudian. The treatises of Captain J. A. Hadfield, W. H. R. Rivers, M. D., and Maurice Nicoll, M.D., savor much more of the teachings of Freud, notably in their conceptions of repression, regression, unconscious mental conflict and the complexes. These writers accept the view that all human relations are sexual in the sense that the sexual instinct is concerned in them. Dr. Rivers deviates a trifle in that he regards "repression" as essentially a conscious activity and believes it probable that underlying every hysterical neurosis there is some degree of amnesia. The third division concerns "The Anxiety Factor" and is discussed in two chapters by Crichton Miller and Maurice Nicoll. The latter's monograph on psycho-analysis is founded upon his belief that "all neuroses are the result of a failure in adaptation on the part of the individual to existing circumstances." The fourth main division deals with "The Management of the Neurotic." W. H. Bryce, M.D., has written a very descriptive section on institutional treatment for the neurasthenic. Millais Culpin, F.R.C.S., has devoted his chapter to the individual treatment of the psychasthenic, the anxiety type, and the hysterical patient.

As a whole the book is of value because it reveals markedly the divergent views of men who have achieved prominence in their individual fields of endeavor, thus demonstrating how little is actually known concerning the mechanisms of the psychoneuroses.

F. H. L.

RADIOGRAPHIC TECHNIQUE. By T. THORNE BAKER, A.M.I.E.E.,  
Pp. 196; 62 illustrations. New York: William Wood & Co.,  
1921.

THE title of this book, *Radiographic Technique*, is misleading. While it contains chapters on the scope of Roentgen-ray work, intensifier screens, localization by radiography, industrial application of the Roentgen-rays, and analysis with the Roentgen-rays, it is essentially a work on the photography of the Roentgen-ray plate and film. In it the author discusses the physics and chemistry of developing, and the cause and avoidance of the faults that result from poor technique. As the author implies in the preface, high-power installation and lavish equipment are no insurance against poor results, yet we would venture the opinion that the average roentgenologist's knowledge of radiographic photography is very meager. While the supply houses are constantly approaching perfection in the production and combination of developing chemicals, and have thus made unnecessary a very thorough knowledge of the science of developing on the part of the radiographer, it cannot be denied, as the author contends, that a knowledge of the principles underlying the production of good negatives is indispensable. We therefore consider this well-written little volume a distinct addition to the technical literature on radiography, and recommend it as a valuable working manual.

J. D. Z.

ACUTE EPIDEMIC ENCEPHALITIS. Pp. 258. 37 illustrations. New York: Paul B. Hoeber, 1921.

THIS book represents the transactions of a new society, the Association for Research in Nervous and Mental Diseases. A unique arrangement will be noticed by the reader of this interesting volume. All the papers read at the meeting of the society were upon one subject—acute epidemic encephalitis. The transactions are so arranged that what each participant in the meeting had to say, either in his paper or in the discussion, upon any particular phase of the subject of encephalitis, is put in one section of the book. For example, the chapter on morbid anatomy is based upon the reports of Drs. Ayer, Spiller, Howe, Boyd and Hassin and includes the answers given by the authors in the discussion. At the end of each chapter are the conclusions of a commission of the society in which the evidence presented is weighed and analyzed. This is the plan of each chapter. The introduction to the book is the presidential address of Dr. Walter Timme. Following this there are seven sections dealing with the history, the symptomatology the diagnosis, the morbid anatomy and the bacteriology of encephalitis. If one wishes to find the present knowledge of encephalitis in a concise and readable form he can do no better than read this book.

A. G. M.

THE CARE OF EYE CASES. By ROBERT HENRY ELLIOTT, M.D., B.S., Sc.D., F.R.C.S., late Superintendent of the Government Ophthalmic Hospital, Madras; Lecturer in Ophthalmology, London School of Tropical Medicine; Ophthalmic Surgeon to the Seamen's Hospital Society, to the Hospital for Tropical Diseases, London, and to the Prince of Wales' Hospital, Tottenham. Pp. 172; 135 illustrations. London: Henry Frowde, Hodder & Stoughton, 1921.

THIS book is written in plain and simple terms, and covers thoroughly the subject treated. It deals only with essential and elementary facts. It should prove very helpful to nurses interested in the care of eye cases, and to the beginner in ophthalmology. One is told how to do properly and efficiently many practical things not usually discussed in the average text-book on ophthalmology.

The contents is divided into three parts. Part I covers briefly the anatomy of the eye, asepsis and antisepsis in ophthalmic surgery, drops, various remedial measures and appliances used in ophthalmic surgery, subconjunctival injections, preparations for an ophthalmic operation, the after-care of patients, and special methods of ophthalmic diagnosis. Part II gives an outline of the principal features of different diseased conditions of the eye and their treatment. Part III gives names of instruments and their use in the principal eye operation. Finally, full-size illustrations and description of all the usual eye instruments are given.

A. G. F.

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ANATOMY OF THE HUMAN ORBIT AND ACCESSORY ORGANS OF VISION. By S. ERNEST WHITNALL, M.A., M.D., B.Ch., M.R.C.S., L.R.C.P., Professor of Anatomy, McGill University, Montreal; late University Demonstrator of Human Anatomy, Oxford. Pp. 428; 195 illustrations. London: Henry Frowde, Hodder & Stoughton, 1921.

It is a pleasure and at the same time highly instructive to review a book of this caliber. As stated in the preface the subject-matter of this work originally formed the substance of a series of lectures given to candidates for the Oxford diploma of ophthalmology, and is here presented in amplified and completed form. One of the chief features of value is the large number of diagrams and photographic illustrations made from a series of dissections and preparations by the author. There are two diagrams in color. As the author states, it is to be regretted that the high cost of color illustrations prohibited their more general use as a means of simplifying the diagrams.

The contents is divided into four parts. Part I, Osteology—the bones forming the orbit, its relations, and the accessory air sinuses of the nose. Part II, Eyelids—the eyebrows, eyelids, conjunctiva, and lacrimal apparatus. Part III, Contents of the Orbit—the globe (external configuration), ocular muscles, bloodvessels and nerves. Part IV, Appendix—the cerebral connections of the nerves. An extensive bibliography and index are included.

The book is well written, and the illustrations are most excellent. The reviewer considers it the best book he has seen on this subject. It should prove of interest not only to the ophthalmologist but also to the rhinologist.

A. G. F.

**THE LIFE OF JACOB HENLE.** By VICTOR ROBINSON, M.D., formerly editor of the *Medical Review of Reviews*; editor of *Medical Life*. Pp. 117. New York City: Medical Life Company, 1921.

THIS short biography of Henle, a great anatomist, is a delightful essay on the life of one whom, at the present time, we in this country know little about. The book may be read not only with profit but also with great entertainment by those who are interested in the lives of the great men in medicine. The book is well printed, with a bright cover, making it a most acceptable little gift for those of our medical friends whom we may wish to remember.

J. H. M., JR.

**THE MEDICAL CLINICS OF NORTH AMERICA.** Pp. 317; 80 illustrations. Philadelphia: W. B. Saunders Company, 1921.

THE Mayo Clinic number of this publication contains, as would be expected, some very interesting and instructive clinics. They are all well presented, terse and decidedly to the point. It is interesting to note, furthermore, that of the twenty-one clinics only two can be called, strictly speaking, statistical reports.

J. H. M., JR.

**THE EARLY DIAGNOSIS OF THE ACUTE ABDOMEN.** By ZACHARY COPE, Surgeon to Out-Patients, St. Mary's Hospital, Paddington; Surgeon to the Bolingbroke Hospital, Wadsworth Common; late Hunterian Professor, Royal College of Surgeons. Pp. 223; 28 illustrations. London: Henry Frowde, Hodder & Stoughton, 1921.

WHILE purists in the English language may take issue at the title of this little volume, those who come in contact with the acute

catastrophes of the abdomen will find but little to criticize in the book. It is a record and summary of the experiences of a surgeon who evidently has had much experience and who has also been a keen observer and clever anatomist. It is refreshing indeed to read a dissertation such as this in which diagnosis is dependent upon the unaided senses alone and not upon a variety of physical appliances.

J. H. M., Jr.

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**EXOPHTHALMIC GOITER.** By WALTER EDMUNDS, Consulting Surgeon to the Prince of Wales's General Hospital, Tottenham, N. Pp. 34; 5 illustrations. London: Baillière, Tindall & Cox, 1921.

THIS small volume is a reprint of a lecture delivered in the North-east London Post-Graduate College by Mr. Edmunds. It is short and succinct. While interesting it hardly seems worthy of perpetuation as an individual bound volume.

J. H. M., Jr.

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**MENTAL HOSPITAL MANUAL.** By JOHN MACARTHUR, M.R.C.S., L.R.C.P., Pp. 212. London: Henry Frowde, Hodder & Stoughton, 1921.

THE purpose of this book is well outlined in the first paragraph of the preface. Written by an Englishman, it is more applicable to the interns of British institutions than to American. It is a good book for the purpose intended.

T. H. W.

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**PRACTICAL PSYCHOLOGY AND PSYCHIATRY.** By C. B. BURR, M.D., Flint, Michigan. Fifth edition. Revised and enlarged. Pp. 257; with illustrations. F. A. Davis Company, Publishers, Philadelphia, 1921.

THIS book is the fifth edition, slightly revised and enlarged, of a manual on the practical applications of psychology and psychiatry for nurses and attendants who deal with the insane. The author, who has conducted a successful institution for many years, is eminently fitted to deal with such a subject. It is not a profound book, but it is not intended to be, for in 257 pages it would be impossible to present the subject adequately.

T. H. W.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE  
UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL  
AND NORTHEASTERN HOSPITALS AND ASSISTANT SURGEON  
TO THE UNIVERSITY HOSPITAL.

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**The Cauterization of Adhesions in Pneumothorax Treatment of Tuberculosis.**—JACOBÆUS (*Surg., Gynec. and Obst.*, 1921, xxxii, 493) describes in detail his technic and reports additional cases. It is found that during the operation it is hemorrhage that one has to fear most, but if the directions given in the technic are followed the author believes that the danger of hemorrhage is small. Pleuritic exudates appeared in about 50 per cent of the cases. These are of two kinds: one comparatively unimportant, which is probably developed by thermal irritation; and one more malignant, which in some cases developed into a tuberculous empyema which resulted fatally in 3 cases. The aim of the operation was attained in all 3 cases of adhesions to the diaphragm, but in only 1 was a corresponding practical and valuable result gained. Complete or sufficient compression of the lung was attained in 27 of 37 cases of adhesions to the apex and lateral chest-walls. From these 30 cases 4 must be deducted in which operation was followed by a complicating serious pleurisy or tuberculous empyema. The early convalescence was favorable in all cases except the 5 mentioned. No *resume* has been made of the lasting results with regard to the pneumothorax treatment in these cases; the author feels, however, that the statistics of the immediate effect of the operation should be sufficient to justify the operation as an adjunct in the pneumothorax treatment of pulmonary tuberculosis.

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**Analysis of the Results of Treatment of Fractures of the Femoral Diaphysis in Children Under Twelve Years of Age.**—SPEED (*Surg., Gynec. and Obstet.*, 1921, xxxii, 527) says that every fractured femur in a child should be given immediate treatment. There is no one set of apparatus nor one angle of traction for all diaphyseal fractures. The most efficient traction that can be devised may fail to give complete



reduction in some cases. The surgeon can get the best reduction possible, obtain union usually with overriding, shortening and changed axial relation of the fragments. Firm bony union will usually follow. According to Wolf's law the bone tends to realign itself when once it is firm and is subjected to weight bearing and muscle stress, so that an excellent functional result may be looked forward to in most cases. Surgical supervision is demanded for at least one year. The only other choice is operative procedure. Lane plates are suggested for fractures, resulting from direct compressional violence, which are transverse or slightly oblique, with overriding of three inches or more, and for which treatment has been delayed. The plate should be removed within six weeks and a walking caliper applied to the limb to hold the reduction gained. Autogenous bone intramedullary pegs are excellent treatment when the patient has reached an age of seven or eight years. As a rule, the fewer operations performed on children's bones, for fresh fracture, the better the average results are in the hands of most surgeons. If a proper Balkan frame and suspension splint traction are used, for femoral shaft fracture in children over four or five years of age, their advantages will be appreciated, for there is constant steady and efficient traction in the axis required against contracting muscles. There is no pain, if the skin surface does not become cut and infected and a traction weight proportionate to the child's body weight is used. The patient has bed freedom to amuse himself and to permit nursing attention. A minimum length and good axial alignment can be obtained by this method if care is given to watching details. Splints permitting knee movements during traction can be used, but most children do not need them—they recover quickly from any knee stiffness acquired during the four weeks of traction. The usual result is much better than a result obtained by any other non-operative method. Direct overhead extension of both legs is recommended for children under four. It is most important that portable Roentgen-ray tubes be used for control of the position gained by traction. The roentgenograms should be made within forty-eight hours after the leg has been established in suspension traction.

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**Focal Infection and Elective Localization of Bacteria in Appendicitis, Ulcer of Stomach, Cholecystitis and Pancreatitis.**—ROSENOW (*Surg., Gyn. and Obstet.*, 1921, xxxiii, 19) says that infections in organs or tissues remote from the surface of the body such as joints, bones and endocardium are conceded by all to be hematogenous in origin. The origin of disease in organs directly or indirectly connected with the surface of the body such as the stomach, gall-bladder, pancreas and appendix is still considered by many to be due, in the main, to direct infection through the mucous membrane lining the intestinal tract or the ducts which drain into it. Many facts suggest that in these too the infection may be blood-borne. The fact that the changes in pancreatitis are usually more marked in the head of the pancreas is quite generally considered evidence of an ascending infection through the ducts. But the author adds that this does not follow, since he has found that the same is true in pancreatitis from intravenous injection of bacteria having affinity for this organ. The place of localization of bacteria after entrance into the blood stream aside from the well-known factor of trauma or the locus minoris resistantiæ has been considered

as more or less accidental. In the infectious diseases, the properties of specific microorganisms determine their localization. Localization in the stomach and duodenum was in general the striking picture following the injection of the streptococcus. The lesions in the gall-bladder were relatively slight. Following injection of the colon bacillus, the picture was reversed. The lesions in the stomach were slight, while those in the gall-bladder were marked.

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**Bone Atrophy: An Experimental and Clinical Study of the Changes in the Bone which Result from Non-use.**—ALLISON (*Surg., Gynec. and Obst.*, 1921, xxxiii, 250) says that the changes in the bone were the same in these experiments in which non-use was produced by nerve paralysis, injury to the joints, and simple fixation. The degree of atrophy of bone was directly proportional to the degree of non-use regardless of the method used to produce the non-use. Simple fixation produced as rapidly developing and as marked bone atrophy as non-use due to section of nerves or injury to joints. Complete fixation of a dog's extremity is so difficult that this method was not extensively employed. There is no evidence warranting the assumption that any disease process plays any role in the production of bone atrophy other than its effect on use. That bone atrophy is not the result of diminished circulation of blood is shown by the fact that bone atrophy rapidly develops in acute inflammatory diseases which limit function of an extremity. The authors have observed a patient who had ligation of the popliteal artery and a diminution of blood supply to the leg sufficient to cause a complete ischemic paralysis and slowly developing gangrene. The tibia, however, showed no evident atrophy after a period of four months. Bone absorption is an active process and the circulation of the blood is necessary to its progress. The process of bone atrophy is not a change in the characteristics of bone as a substance. The process of bone atrophy is a change in the amount of bone present. This affects the size, shape, thickness, length, weight and texture of the whole bone and accounts for its changes in gross anatomy.

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**Multiple Pleychondromata.**—WIDMAN (*Am. Jour. Roent.*, 1921, iii, 462) says that the condition is a definite pathological entity due to an anomaly in ossification of temporary cartilage. There is as yet considerable variance of opinion as to its etiology. Etenfried characterizes the conditions as to the occurrence of multiple more or less symmetrical cartilaginous and osteocartilaginous growths within and on the skeletal system, generally benign and resulting from a disturbance in the proliferation of the bone-forming cartilage. There are endocrine derangements—trophic disturbances depending upon disease of the central nervous system.

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**Pernicious Anemia with Special Reference to the Spleen and the Large Intestine.**—MAYO (*Ann. Surg.*, September, 1921, lxxiv, 355) says that Eppinger's work at least demonstrated that the removal of the spleen initiated striking temporary improvement. Previous to 1917 fifty splenectomies had been performed in the clinic for definitely established pernicious anemia. Further, for three and a half years, the procedure has been discontinued, since it was not thought to give a

degree of palliation sufficiently greater than that following blood transfusion. It has been found in at least one-third of the cases that the average life of the patients is greatly prolonged, while in about 10 per cent the prolongation is sufficient to lead to the hope that cures may result in some cases. Apparently removal of the spleen stops red-blood cell destruction but does not greatly affect the disease otherwise. Many observers have expressed the belief that toxic materials from the gastro-intestinal tract are the cause of pernicious anemia, and if this be true the probable location of this absorption would be in the proximal half of the large intestine. Experience with a large number of resections for relief of such patients has shown a comparatively low mortality and a high percentage of permanent cures.

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## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
OF PHILADELPHIA.

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**The Effect of Compressed Yeast Cake in Infant-feeding.**—LADD (*Arch. Ped.*, December, 1921) says that the general statement may be accepted that food for an infant must have three known vitamins, fat-soluble A, water-soluble B and antiscorbutic, and these must be present in sufficient amounts. It is just as important to have sufficient amounts of fats, carbohydrates and proteins, mineral matter and water to meet the individual needs. The writer states that infant feeding has reached a point that it is a rare exception that a normal baby cannot be successfully reared on cows' milk when properly adapted to the needs of the infant. A large amount of experimental feeding has been carried out on the lower animals to determine the part played by these three vitamins in the general problem of nutrition, and there have resulted many valuable suggestions to the principles of infant feeding. Osborne and Mendel have shown very clearly that their experimental rats fail to show normal growth gain on milk, but that a small amount of yeast promoted normal growth. In the 10 cases studied by the writer the problem was to determine whether the addition of such an accessory as yeast, which is presumably rich in water-soluble B vitamin, would favorably influence the development of infants in the first year, or undernourished babies in the second year, the other factors being managed along lines of rational feeding. As a result of the observations it was found that only 2 out of the 10 cases showed an increased rate of gain when yeast was incorporated in the food and in these other factors in the food probably accounted for the difference. In the other 8 cases the yeast was apparently inert, with one exception that when given raw it produced a definite fermental diarrhea. There was no clinical evidence that the appetite or general condition of the child was better during the period of time when the yeast was given.

**The Serum Prophylaxis of Measles.**—MCNEAL (*Jour. Am. Med. Assn.*, February 4, 1922), in a small epidemic, injected serum taken from donors who were free of tuberculosis and syphilis, and had passed through fairly severe attacks of measles without complications or sequelæ. Sixteen children exposed to measles received intramuscular injections of 5 cc of serum obtained as noted above five to nine days after the disappearance of the fever. Twelve of the 16 children injected remained free from measles and 4 developed a mild form of the disease. One child developed measles after two months successful injection, which suggested that the immunity does not persist longer than sixty days in some cases. The method recommends itself most highly for the prevention of measles during the period of danger, between the ages of five months and six years, in tuberculous children and in those physically below normal. In institutions in which large numbers of frail children are intimately associated the procedure should be of great value. A marked attenuation of the disease with permanent immunity, but without complications or sequelæ would seem to be even more advantageous than the absolute protection.

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**A Dietary Consideration of Eczema in Younger Children.**—O'KEEFE (*Jour. Am. Med. Assn.*, February 18, 1922) indicates that eczema is more and more considered to be not entirely a skin disease, but rather a systemic condition whose chief manifestation is chiefly cutaneous. He says that faulty digestion of protein with consequent absorption in an undigested state is the most striking common feature in these cases of eczema. He says that the sensitization of the nursling does occur through foreign proteids ingested with breast milk. The aim of treatment should be to secure complete digestion of the ingested protein, either by improving the digestive function or by limiting the intake of the offending protein. An analysis of the results of this treatment, combined with external remedies, showed that 17 of the 41 patients had been relieved of their trouble entirely. In 14 of this 17 the time elapsing between the beginning of the treatment and the clearing of the skin could be definitely determined. In the exclusively breast-fed there was an apparent cure in 40 per cent and a definite cure in about 20 per cent following the omission or limiting of certain articles of food in the maternal diet.

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**Is There More than One Kind of Rickets?**—SHIPLEY, PARK, McCOLLUM and SIMMONDS (*Am. Jour. Dis. Children*, February, 1922) say that their experiments make it clear that when the rat is deprived of certain active light rays and unidentified factors contained in cod-liver oil a pathological condition corresponding to rickets in human beings, in all the fundamental respects, can be produced through the diet. This can be done in two ways: The phosphorus may be diminished and calcium may be supplied in the optimal quantities or in excess. Another way is by reducing the calcium and maintaining the phosphorus at a concentration near the optimum. They believe it to be certain that in the human being similarly deprived of light and the unidentified factor it would also be possible to produce true rickets through an adjustment of the calcium and the phosphorus of the diet in the two ways mentioned. As a result of their experiments

they are led to believe that there are two main kinds of rickets: One is characterized by a normal or nearly normal blood calcium and a low blood phosphorus, which may be called a "low-phosphorus rickets." The other is characterized by a normal or nearly normal blood phosphorus, but a low-blood calcium, and may be called "low-calcium rickets." If the hypothesis is correct the relation of tetany to rickets would appear to be essentially an expression on the part of the nervous tissues of an insufficiency of the calcium ion. Rickets is essentially an expression on the part of the skeleton of disturbed relation between the calcium and phosphate ions in the body fluids. Tetany is frequently associated with rickets because rickets is a disease in which the calcium ion in the body tissues and fluids is subject to variation. Tetany occurs independently of rickets, just as rickets may occur independently of tetany. Since tetany may occur with the low-phosphorus form of rickets, it does not serve to differentiate one from the other. Tetany is essentially associated with the low-calcium form of rickets and for all practical purposes the low-calcium form is the rickets of tetany. It seems possible that the etiology of rickets may be as varied as the etiology of tetany. Their experiments suggested that in the absence of certain active light rays and an unidentified dietary factor contained in cod-liver oil any influence which would result in the depression of the calcium or phosphate ions in the body fluids, with the formation of calcium-phosphate ratios favorable for the development of rickets, would ultimately produce the disease. There may be several influences. As the result of clinical observations concerning curious associations of rickets with other pathological conditions, and certain peculiar manifestations of the disease in some children, there is a possibility that there may be a true renal rickets, and that the rickets accompanying the alimentary anemias may represent a somewhat different form of the disturbance in metabolism from what is present in the ordinary forms of the disease.

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**The Value of the Routine Use of the Colloidal-gold Reaction in Acute Epidemic Poliomyelitis.**—REGAN and CHENEY (*Am. Jour. Dis. Children*, February, 1922) performed this test on 74 spinal fluids from 21 cases of this disease. The fluid was examined at intervals varying from the fourth to the one hundred and twenty-third day. The predominant type of the malady was the myelitic with a high proportion of cases presenting symptoms of moderate or marked polyneuritis. The curves obtained were classified according to the week of the disease in which the spinal fluids were taken. It was found that there was always a reaction with colloidal-gold solution in the case of every poliomyelitic fluid examined during the acute stage of the disease. The average curves for the first and second weeks of the disease were very similar, presenting a graduated increase in the reduction of ascending dilutions of spinal fluid, starting in the reddish-blue area in 1:10, extending into the lilac or purple area in 1:40 to 1:80, and then descending somewhat more abruptly in the reddish-blue in 1:160 and reaching the non-reducing or red color at 1:640. In the latter weeks of the malady the average curve gradually subsided, reading normal in a minor proportion of cases, 3 out of 10, by the eighth or ninth week; while in the remaining 70 per cent, or 7 cases, the curve

remained elevated at the ninth week. In 2 cases, 1 in the fourteenth and the other in the eighteenth week, the curve was still elevated in both. In 1 chronic case they found the typical curve still present five years after the initial attack, but the history indicated several relapses. Of the 3 cases, in which the curve reached normal before the end of the eighth week, this occurred on the twenty-eighth, fifty-third and fifty-fifth days respectively. When the curve had once reached normal it was not elevated again in the 3 cases studied. Cases presenting a persistence of the very acute curve of the first few weeks up into the ninth week or beyond commonly presented at this time either considerable residual paralysis with slight, moderate or marked polyneuritis, or else slight paralysis with a polyneuritis of a marked type. A definite persistence of the acute hydrocephalus usually remains in these cases. There seems to be a relationship between the duration of the positive colloidal-gold curve and the acute inflammatory stage of the disease, so that when the reduction of gold chloride becomes normal, the acute period is over. This is important from the standpoint of active therapeutic measures for the subacute stage. With gradual subsidence of the colloidal-gold curve there is usually a corresponding improvement in the general condition of the patient in the paralysis and meningeal symptoms. This relationship does not always hold true, and in patients with marked polyneuritis the curve may remain elevated after the subsidence of the paralysis. There was no close relationship between cytology and chemistry of the spinal fluid and the colloidal-gold reaction.

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**Colic in Breast-fed Babies as a Result of Sensitization to Foods in the Mother's Dietary.**—SHANNON (*Arch. Ped.*, December, 1921) cites a number of cases illustrating his contention that elements in the diet of the mother may be the cause of colic in the offspring because of some peculiar susceptibility of the baby to certain foods. He points out that the mother's milk transmits foods that the mother eats, and that these foods may produce disturbances in the infant. Persistent colic in breast-fed babies is frequently due to sensitization to foods that the mother eats, and which comes to the infant through the breast milk. Removal of these foods from the diet of the mother will frequently result in permanent cure of the colic. Food allergy is a rational basis for explanation of the well-known statement that all breast milk is not the best food for every baby. The fact that one infant will thrive on breast milk that another cannot tolerate is explained on the basis of allergy to foods contained in the breast milk. Recognition and application of these principles will result in the prevention of considerable suffering in the baby and occasionally will remove the necessity of too early weaning from the breast.

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**Excess Protein and Mammary Secretion.**—HARTWELL (*Biochem. Jour.*, 1921, vol. xv) had observed previously that a diet containing 40 per cent protein by dried weight fed to nursing rats was detrimental to the young, and in this study he confirms that observation. He also found that the same result ensued from commercial edestin, blood and egg albumin, gelatin and home-made gluten. Such dietaries apparently render the milk poisonous, and finally checks its flow.

Home-made fish and meat protein do not always cause such harmful results as edestin, albumin and gelatin, but in some cases the litters died with typical symptoms. In others the baby rats survived, but only a few were normal. In spite of the ultimate ill effect of edestin and caseinogen, the immediate results of its addition to bread was to produce a maximal growth curve of the young. Other proteins produced slower growth. Toxicity was not shown for ten to eleven days. The toxicity of the mother's milk was demonstrated by spasms and allied symptoms. The cessation of the flow of the milk was shown by the litter's loss of weight, and the symptoms of a like nature and by the emptiness of the alimentary tracts. There was some correlation between increase in the weight of the mother and danger to the offspring. When the mother put on weight the sucklings suffered. As regards gelatin, it caused loss of weight of the mother and the offspring died. It seemed unlikely that an absence of vitamins was the cause of this, because a rat can bring up a healthy litter on a diet of white bread alone.

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## OBSTETRICS

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UNDER THE CHARGE OF

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**Heart Disease Complicating Pregnancy.**—WERNER (*Arch. f. Gynäk.*, 1921, cv, 41) has studied 7626 cases of pregnancy and labor to determine the frequency and the history of diseases of the heart. Among these were found 67 cases of heart lesions, of which 63 were valvular; 4 showed extensive changes in the heart and alteration in the ascending aorta. Of these 67 cases, 31 were uncomplicated mitral insufficiency, 12 were uncomplicated mitral stenosis, 19 were mitral insufficiency combined with mitral stenosis and 5 were other varieties of heart lesions—including those of the aortic orifice. An effort was made to trace the history of these patients after they left the Clinic, but it was possible in only 12 of the cases. The mortality was 4.5 per cent among the 67 cases. To illustrate the important conditions in these cases the writer gives the history of a primipara, aged twenty-five years, who at nine and nineteen years had inflammation of the joints and disturbed respiration. She came to the clinic in the second month of pregnancy with disturbance of breathing, slightly enlarged liver and spleen and slight icterus. After two weeks' treatment in the hospital she was very much improved, but after leaving hospital she grew worse; it was finally necessary to produce therapeutic abortion. A year and a half after she was examined, when it was found that she had a mitral stenosis (not fully compensated) with moderate cyanosis, slight jaundice and enlargement of the liver. The case illustrates the subsequent history of this patient and how a temporary improvement, produced by rest and drugs, rarely continues for any length of time.

One of the fatal cases was a primipara, aged twenty-seven years who had had a diseased heart since she was sixteen and came first to the clinic in the second month of pregnancy. As her condition was growing worse therapeutic abortion was performed. After eight days of rest in bed and treatment with digitalis the heart condition improved. The patient was discharged from the hospital and died at her home three weeks afterward from failure of the heart action and dropsy. In the other 2 fatal cases autopsy showed extensive changes in the circulatory apparatus outside of the heart. In the 31 cases of mitral insufficiency symptoms of decompensation occurred during pregnancy or labor in 18. In 8 these symptoms appeared in the first half of pregnancy, and in 10 in the second half. In the 12 cases of mitral stenosis there were disturbances of compensation in 10, and it was interesting to observe that such complication was more frequent in the first half than in the second half of pregnancy. It did not seem to be the size and weight of the full-term uterus which affected the heart, but certain other conditions in early pregnancy. In mitral stenosis of severe character the muscle of the left ventricle is damaged, and also the capillaries of the lungs, which accounts for the occurrence of the failing heart in early pregnancy. Of 19 cases of mitral insufficiency combined with stenosis 14 had symptoms of decompensation earlier or later in the pregnancy; 7 of these in the first half, 6 in the second and in 1 the beginning of decompensation was not accurately noted. Of the 5 cases of aortic disease 4 had more or less cardiac disturbance in the early part of pregnancy. There were 22 full-term living children born to the 31 women having mitral insufficiency. There were 20 spontaneous labors and 2 pregnancies were terminated by operation—1 by Cesarean section and 1 by forceps. There were 2 dead-born children, craniotomy having been done on one after the child had perished from pressure during birth. In another case the child died during labor from birth pressure but was finally delivered, postpartum hemorrhage complicating the last part of the labor. In 3 of these patients labor came spontaneously but before full term. One was a case of twins, and in the other 2 the children were viable. There was 1 abortion at six months, 3 cases of hydramnios, 1 with transverse position of the head in labor, and one where the rotation of the head failed, although upon the pelvic floor. In 4 cases the placenta was removed by the hand, and in 1 case it was forcibly expressed. One patient had fever during the puerperal period but recovered. Because of the condition of the heart section was done in 1 case; in a second, section with resection of the tubes. Two patients came into the clinic with heart lesions, but went out before they had been delivered. In the cases of mitral insufficiency it was necessary to interrupt the pregnancy in none. Cesarean section was performed in 1 case because of threatened heart failure. In this patient sterilization was done by resecting the tubes. In the 12 cases of mitral stenosis, 6 full-term living children were born in spontaneous labor. There was 1 birth of a macerated fetus, and in 2 cases it was necessary to interfere because of the cardiac condition, therapeutic abortion being done in 1 and abortion accompanied by curetting in another. In 3 cases patients improved so much that pregnancy was not interrupted and they left the hospital. There



were 19 patients who had combined cardiac lesions—insufficiency plus stenosis. Among these were born 6 children without any abnormality occurring during birth. One was delivered by forceps; 1 child was born macerated (the mother giving a negative Wassermann reaction). There were 6 spontaneous premature labors. Because of the cardiac condition it was necessary to interfere five times with these patients. One of these patients passed out from observation so that her final health is unknown. In 1 of the aortic cases the patient had had rheumatism and swollen joints for nearly thirty years. She had had seven previous pregnancies without a history of complications on the side of the heart. So soon as the last pregnancy began she had headache and faintness, specks before the eyes, difficulty of breathing and edema. She died four weeks before full term with sudden collapse of the heart. At autopsy the heart was found hypertrophied with fluid in the chest and pericardium. There were also lesions in the endocardium about the aortic valve. The aortic orifice was narrow. It was observed that one of the best signs of impending death in these patients was severe disturbance of respiration. In the aortic cases the dangerous elements seemed to be the degeneration of the heart muscle, and this might produce unexpected and sudden death at any time. This seemed to be the most serious lesion which these patients had and least susceptible to improvement by treatment. His experience shows that in mitral stenosis complicating pregnancy that pregnancy should be interrupted at the first sign of decompensation. Medical treatment should not be continued unless markedly successful, because whatever is gained thereby is of very brief duration and valuable time is lost by medical treatment. Where there is disease of the circulatory apparatus outside the heart the condition seems to resemble in severity mitral stenosis. In cases of aortic disease the danger increases with each successive pregnancy.

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**The Function of the Kidneys in Pregnant and Puerperal Women.**  
—WERNER (*Arch. f. Gynäk.*, 1921, cv, 63) has studied healthy parturient women, pregnant women with heart lesions, with glycosuria, with albuminuria, with chronic nephritis and with eclampsia. His purpose was to study the excretion of saline material by the kidneys. In pregnancy there was great variation—from 7 to 26 gm. daily—in puerperal patients from 11 to 21. If the results of investigations in these varying sorts of cases are considered, the most significant feature lies in the fact that the greatest disturbance in the function of the kidneys occurs in those pregnant women who have severe albuminuria. This is seen in the excretion of salt and of water. The excretion of salt is very much reduced and concentration of the urine also lessened. The correspondence between the lack of excretion and the diminished concentration is very striking. The percentage of saline falls decidedly, while the percentage of water increases somewhat. The excretion of water is considerably less than the intake. If the patient is given water, this difference is very much increased. From these facts it is evident that there is some marked insufficiency of the kidneys to both the excretion of salt and of water. While the excretion of these substances may be greatly reduced nitrogenous matter is excreted at a normal rate, although the percentage of concentration is somewhat

reduced. After labor occurs there is a rapid change. In the first days of the puerperal period the quantity of salt—in absolute quantity and in concentration—is considerable, and the excretion of water is greater than the intake. Apparently the kidneys are excreting salt and water which have been retained during pregnancy. So great is the elasticity of healthy organs that great variations in the quantity and concentration of ratios and the salt excreted are observed. In mild cases of albuminuria in pregnancy similar disturbances to those observed in severe cases are also seen. There is often increased excretion of salt and water. This can be explained by the fact that in these cases the rest in bed, which the patient has, is enough to stimulate kidneys (not badly damaged) to resume their normal function. This also explains the benefit seen in repeated pregnancy when a patient is kept in bed, and also in complicated and severe cases when the patient is in bed for some time. So far as these phenomena are concerned it is evident that in the first days after the birth of the child they resemble the more serious cases of albuminuria during pregnancy. It is also interesting to note that there seems to be no special disturbance in the excretion of nitrogenous material. In the late days of the puerperal period there is a constant improvement in the excretion of salt and of water, which seems to result from improved function in the kidney. One can scarcely distinguish between the phenomena natural to the puerperal period and those sometimes seen in albuminuria and nephritis. Cases of eclampsia resembled those of albuminuria in pregnancy. In two-thirds of the patients salt and water seemed to be excreted fairly well. In one-third excretion was much reduced. These were the cases which had severe eclampsia before labor and which were examined just after confinement. The concentration and the dilution function of the kidneys seemed in all these patients to be well performed. After eclampsia the kidneys resumed their functions more slowly; and after albuminuria the process resembled more what is seen in chronic nephritis. In cases of heart disease without compensation there was marked failure of the concentration and dilution function of the kidney. This was not so well-marked as in albuminuria, but the nitrogenous metabolism was also disturbed and seemed to be deficient if one should judge from the urine. The resumption of function after labor was gradual and slow. This can readily be understood when it is remembered that decompensation in these cases does not cease immediately after labor, but may occupy days or weeks. In glycosuria the kidneys are more overburdened than in healthy patients. The quantity of urine and the quantity of fluid taken are greater. Complications arise which are in slight measure only to be estimated by the excretion of saline. It is evident, however, that concentration and excretion are much less than in normal conditions. It is interesting to note that variations in the excretion of salt, nitrogen and water by the kidneys seemed to be practically the same in albuminuria, nephritis and eclampsia and that these differ only in intensity, in the rapidity of their development and also in the rapidity of their disappearance. In the case of diseases of the heart the excretion of nitrogenous material is very much disturbed. When glycosuria is present and the intake and excretion of water are increased, salt is excreted in moderate degree only, and usually in

lessened amount. There seems to be a common element in these phenomena, pointing to disturbances of the kidney. There are very great variations in the excretory action and in the concentration of the secretion in healthy pregnant and parturient women; and this variation occurs in different days and different times of the day. In cases where there are well-marked pathologic conditions the element of disturbance in kidney function may become very pronounced, and in these cases the power of the kidney to adapt itself to changed conditions seems to be lost.

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## GYNECOLOGY

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UNDER THE CHARGE OF

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**Radiotherapy of Non-malignant Menorrhagia.**—The present status of radiotherapy of non-malignant uterine bleeding has been fairly well summarized by GRAVES (*Surg. Clinics of North America*, June, 1921, p. 620), who reminds us that before the advent of radium uterine bleeding in adolescence and young womanhood presented a baffling problem. The etiology of this condition has never been solved. One may speak of ovarian hyperfunction as a cause, but the term is based on the vaguest kind of knowledge and even if it is correctly used it is of no assistance in the problem of treatment. The various remedies for this condition, such as animal serums, gland extracts like pituitrin, the various styptics, iron, arsenic, etc., are all of very equivocal value and repeated curettings are equally useless. The bleeding not infrequently continues for years, and may reduce the patient to an extreme state of anemia, in a number of cases the writer being obliged to resort to hysterectomy and castration. In the earlier days of radium, as a therapeutic agent, it was applied only for the menorrhagias of women comparatively near the menopause. Operators were fearful of using it in young women on account of the danger of bringing about an artificial menopause. It was soon discovered that when radium was given in moderate dosage excessive menstruation may be diminished and regulated with a fair degree of certainty. Therefore, at the present time it is employed without hesitation for urgent cases even in pubescent girls. In making the decision as to the treatment of a very young patient, the question of the danger of causing a complete cessation of the menses has been a most important one, but the writer is convinced by experience that a dosage of 25 mg. for from four to six hours may be given with entire safety and he believes that it is quite probable that the ovaries of the young are able to withstand a

greater exposure to radiation without losing their function than are the ovaries of older women. In regard to the manner in which radium produces its effect, he believes, with many others, that the rays exert an influence both on the endometrium as well as on the ovaries. The exact effect on the endometrium has not been determined since microscopical examination of the uteri, removed after unsuccessful treatment with radium revealed no very definite changes. One would expect a sclerosis of the stroma which might bring about a temporary or permanent obliteration of the endometrial capillaries. Radium given in sufficiently large doses is capable of destroying the Graafian follicles as has been shown by the examination of ovaries removed after radium treatment. The extent of the destruction of the follicles depends on the size and length of time of dosage and also on the age of the patient. The primordial follicles are formed near the center of the ovary and as they develop they migrate toward the surface, finally culminating in a ripe corpus luteum or an atretic follicle. A large dose of radium is sufficient to destroy all of the follicles in the ovary both young and old, but it may be imagined that a moderate exposure of the radium may kill only the older and riper follicles that are near the surface while the younger and less-developed bodies escape its influence. In this way may be explained those cases in which the menstrual function is suspended for several months, only to be resumed in a natural manner. In other words, menstruation ceases during the period of time required by the younger follicles to mature. The fact that the menstruation is in most cases restored without the abnormal bleeding which before characterized it may be explained by some minute but permanent change in the endometrium.

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**Histological Study of Radium Effect on Cancer.**—The exact effect of radium treatment upon the carcinoma cells, as determined by histological studies of radiated tissues, has been determined by NORRIS and ROTHCHILD (*Am. Jour. Roent.*, 1921, 8, 604), who divide the histological pictures into five stages. The first stage is that of acute inflammatory reaction and embraces the first week after radiation. During this stage there is a congestion of the bloodvessels, exudation of lymphocytes and polymorphonuclear leukocytes and a slight edema of the stroma. A slight swelling of the cancer cells is noted, also slight enlargement of the endothelium of the bloodvessels. The second period embraces the second week and is the stage of early nuclear and cytoplasmic changes. This stage shows a gradual swelling of the cancer cells, an enlargement of the nuclei and relative increase of the cytoplasm. Mitosis in many instances ceases and the nuclear substance appears as granules, while the cytoplasm at times shows vacuolization. At the beginning of the third week, the stage of intercellular changes, young fibroblasts are found scattered throughout the radiated area. They infiltrate the malignant cells, dividing them into strands and in many instances completely surrounding groups of cancer cells and isolating them. The lymphocytic infiltration is increased in this stage, although lymphocytes and leukocytes have been present during the first two periods. The bloodvessels show edema of all the coats and especially of the intima, with almost complete obliteration of the lumen. At times leukocytes are present in

the vessel wall. The stage of destruction starts with the fourth week after the application of the radium and continues to the ninth week. The nuclei of the malignant cells may be broken up and in many instances found as masses of chromatin, while, on the other hand, they may shrink and appear as an egg in a nest. The cytoplasm undergoes cytolysis. The group of cancer cells, which have been isolated by the fibroblasts and connective tissue show a numerical reduction. The fibrous overgrowth at the end of this period is conspicuous. In its meshes the young bloodvessels at times show constriction of the lumen, while the malignant cells throughout the entire field are considerably reduced numerically and in size. In the final period or stage of healing, the cancer cells appear as compressed bands in the fibrous stroma, only the small contracted nuclei remaining. At a later period no remains of the malignant cells are noted. Ultimately, the surface epithelium shows regeneration. The features of these changes are the changes of the malignant cells with their destruction and ultimate absorption and the replacement of fibrous tissue. While the histological pictures have been divided into five stages, it must be acknowledged that the stages blend, and one may find many instances of early cellular changes with cells in the stage of destruction.

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**End-results of Operations for Relaxed Pelvic Floor.**—The final results in operations performed for various types of relaxed pelvic floor have been analyzed in a series of 60 cases by CUTLER and JAMESON (*Arch. Surg.*, 1922, 4, 173), of the Peter Bent Brigham Hospital. They state that the etiological factors may be, and are many, just as with other types of hernia; but congenital defects and trauma stand out as the principal causes, and one or both are usually present. Congenital conditions undoubtedly constitute a considerable factor, as nulliparas with complete prolapse have been reported. Trauma is probably of greater importance but the factor of increased intra-abdominal pressure, whether due to tumor, ascites or straining at stool, seems to be of only contributory importance. For purposes of study the following arbitrary classification appeared most convenient: Group I, women in the child-bearing age; Group II, women past the child-bearing age. The dividing line cannot correspond to the biological limit, since it seems reasonable to include in Group II women near the menopause who do not desire more children and those with serious organic diseases, such as cardiac or renal disease, in whom future pregnancies would be a serious menace to life. Each group is further subdivided into Class A, vaginal prolapse (cystocele and rectocele), in which the uterus is in its normal relation; Class B, vaginal and uterine prolapse, in which there is some degree of uterine descent; and Class C, procidentia, in which there is uterine prolapse with the uterus outside. The class of patients with uncomplicated vaginal prolapse treated by local plastic procedures shows surprisingly good results; better in the group of patients examined than in those reporting by letter. This interpretation of results was possibly influenced by rigid insistence on anatomical cures at the final observation. The reason why cases of this type do not go on to uterine prolapse is not clear; but it appears that there may be cases in which local trauma permits of a local herniation without actually destroying the

supporting power of the pelvic floor. It is well recognized that cases with complete perineal tears frequently do not progress to uterine prolapse. Possibly the good results in this group will be partially vitiated with time. The results seem, however, to indicate that when uterine prolapse is to accompany vaginal prolapse it commences simultaneously with the vaginal lesion, and that if, therefore, patients at examination show no uterine prolapse, they can be permanently relieved by local vaginal operations. Retroversion may be considered as the initial stage of uterine prolapse. The class of patients with uterine and vaginal prolapse (Class B) show less satisfactory results. Of the patients reporting for examination, those in Group I showed satisfactory results, those in Group II unsatisfactory results (10 recurrences in 24 cases). Among the patients reporting by letter in Group I, 2 patients in 7 were unrelieved and in Group II, 3 patients in 8 were unrelieved. Certain of the failures can be explained by unwise choice of operative procedure. Thus, in patients of this class, in whom a simple repair or an abdominal operation alone was performed, there was frequently recurrence; and when a combined operation was performed, the abdominal procedure being simple Gilliam or other suspension or fixation operation, there were several recurrences. A combined operation, in which the abdominal procedure was either some form of hysterectomy or a Moschcowitz procedure, proved satisfactory. It appears, therefore, that a combined local repair and abdominal operation should be performed when uterine and vaginal prolapse are present. The type of abdominal procedure to be employed may depend on whether the patient desires more children. It is recognized that the Gilliam operation and even ventro-fixation of the fundus do not endanger subsequent pregnancies. It is also accepted, and these results seem to coincide with this view, that such operations do not give a high percentage of successes in uterine prolapse. The Moschcowitz procedure also permits of subsequent pregnancies, and these results demonstrate its efficacy in this class of patients. In Group II, when future child-bearing is of no importance, a wider range of operations is available and the findings in this series agree with the opinions of others that supravaginal hysterectomy, with either ligamentous suspension or ventro-fixation of the stump, is most efficacious. In procidentia cases, Class C, the results have been equally discouraging. Four of the 9 patients who returned for examination had recurrences and 2 of the 4 patients replying by letter were unrelieved; 6 failures in 13 cases (almost 50 per cent). Here again uncombined operations resulted badly, patients on whom even such a radical abdominal procedure as bisection of the uterus was performed returning for examination with most distressing vaginal prolapse. Patients on whom a hysterectomy or the Moschcowitz procedure was performed, in combination with a vaginal repair, usually did well, and the removal of the uterus either from above or by vagina after the Mayo procedure has proved satisfactory. The necessity of combined operations and radical abdominal interference is again demonstrated. The type of operation is now and then further influenced by the condition of the patient. It must be remembered, however, that the combined operation need not be performed at the same sitting. They have frequently been performed separately, usually with an

interval of from a week to ten days, but sometimes after some weeks, the patient returning for the second stage when thoroughly rested. The vaginal procedure is necessarily performed first. The task set is never a simple one and the patient must be made to understand this from the beginning.

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## PATHOLOGY AND BACTERIOLOGY

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**The Fate of Killed Non-hemolytic Streptococci Injected into the Blood, and the Resulting Cellular Changes.**—NAGAO (*Jour. Infect. Dis.*, 1920, xxvii, 327) injected 2.5 cc formaldehyde-killed, non-hemolytic streptococci suspended in salt solution into the jugular vein or left ventricle of 300 gm. guinea-pigs. The animals were killed immediately after injection or at intervals of five, ten and thirty minutes and in one, two, six, twelve, forty-eight, seventy-two and ninety-six hours. The various organs were fixed in Zenker's fluid and stained with Delafield's hematoxylin and eosin and a modification of the Gram-Weigert method. It was found that those organisms which were injected into the jugular vein accumulated principally in the lungs, the remaining ones being taken up by endothelial cells in the liver and by endothelial and other cells in the spleen. Injection into the left ventricle and portal vein also resulted in cocci collecting to some extent in the lung. The author believes that the accumulation of cocci in the lung is largely mechanical and the result of the formation of masses of cocci in the blood on one hand and the narrowness of the lung capillaries on the other. In the lung the bacteria were phagocyted mostly by polymorphonuclear leukocytes and to a much less degree of mononuclear and endothelial cells. The leukocytes were actively phagocytic, engulfing the bacteria within about ten minutes after injection. In from thirty to sixty minutes the phagocytic leukocytes left the lungs, the majority going to liver and spleen, where there was great increase in such cells up to six hours after injection. In contradistinction to the lung, the hepatic endothelial cells were very active in phagocytosis, more so than the cells of spleen. The writer regards the liver as the most important place of elimination of bacteria, the spleen being next. The fixed cells of the bone-marrow were not as active but in the marrow an active supply of new leukocytes developed soon after injection from the myelocytes. Apparently the plasma cells that appeared in the spleen and other organs following the injection were produced locally, probably arising from existing

perithelial lymphoid cells and from immigrated lymphocytes. He believes that plasma cells do not come from the fixed cells of connective tissue. As early as ten minutes after injection there were varying degrees of hyperleukocytosis in blood of the right ventricle and the lungs which was interpreted in terms of a local positive chemotaxis produced by the bacteria and the products of cellular disintegration. Disarrangement of the normal Arneth's scale began promptly after the injection and reached its maximum in about three hours. It is the belief of the author that, in infectious diseases, hyperleukocytosis or leukopenia is not a danger sign provided the blood presents the normal leukocytic picture but marked displacement to the left in Arneth's count, especially when associated with diminution in the number of leukocytes is a danger sign, indicating exhaustion of the leukocytogenic function of marrow.

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**The Fate of India-ink Injected into the Blood. II. The Formation of Intracellular Granules and Their Movements.**—In a second communication, NAGAO (*Jour. Infect. Dis.*, 1921, xxviii, 294) reported observations made after the injection of India-ink suspensions into rabbits and guinea-pigs. The particles of India-ink seemed to be absorbed by elements in the cells, probably granules, a capsule of ink particles being formed which was designated as the primary ink granule. In a few days the primary granule became irregular, forming the secondary ink granule. As the cell disintegrated these granules became mixed with debris and frequently coalesced to form the tertiary granule. Most, if not all, cells that took up ink granules underwent a rapid destruction, which was associated with vacuolation, beginning about the ink granules and extending gradually. The disintegration of the cell was in direct ratio to the number of granules it contained and set free the ink granules, which, the writer believes, were not excreted by special cell function. The phagocytic leukocytes transported granules to some extent and could carry them to the outside of the body, but the main movement of the ink granule was by way of the blood and lymph stream, acting on granules freed from disintegrated cells, such cells sometimes being taken up by phagocytic cells with which they came into contact. The injection of chemotactic solution into the peritoneal cavity resulted in the attraction of cells with few ink granules only. Apparently phagocytes stuffed with granules were not able to migrate and the ink leukocytes that form in the peritoneal cavity did not seem to be able to return to the blood. The ink granules were transferred in small degree only to the blood by way of the lymph in the earlier stages and formed primary granules in the liver, spleen, etc. The mechanism of the accumulation of ink granules in the interior of cells seemed to be similar to that of vital staining by soluble dye, being governed largely by physical conditions.

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**The Heat Resistance of Spores with Special Reference to the Spores of B. Botulinus.**—In a study involving the effect of hydrogen and hydroxyl-ion concentration on thermal resistance and the effect of numbers, desiccation, age and the presence of sodium chloride on the spores of sixteen representative strains of *B. botulinus*, WEISS (*Jour. Infect. Dis.*, 1921, xvii, 70) found that the free spores were killed within



five hours at 100° C., within forty minutes at 105° C. and within six minutes at 120° C. The destruction of the spore was a gradual process, being probably due to a slow protein coagulation. Young moist spores were more resistant to heat than old moist spores. The thermal resistance of emulsions of young spores increased as the concentration of the emulsion increased. Sodium chloride lowered the thermal resistance in direct proportion to the increase of the salt concentration. The hydrogen and hydroxyl-ion lowered the thermal resistance, the rate of reduction decreasing as the concentration increased. Media in which *B. botulinus* was growing stabilized themselves at a point near a Ph value of 7.5. The author believes that, in processing canned foods, it is necessary to determine the Ph value of the material to be sterilized immediately before exposure and that in all practical processing methods a goodly safety factor should be allowed.

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**Study of Transfused Blood. I. The Periodicity in Eliminative Activity Shown by the Organism.**—If a parallelism between the elimination of transfused blood and normal blood destruction can be drawn, ASHBY (*Jour. Exper. Med.*, 1921, xxxiv, 127) feels that the process is associated with the activity of the endocrine gland system. The elimination of transfused blood was studied in human beings in Group I, II and III, receiving Group IV transfusions by mixing the recipient's blood after transfusion with Group IV serum—a procedure which agglutinates the native erythrocytes, leaving the transfused corpuscles free and capable of being counted in a hemocytometer. It was found that the length of time that transfused blood remains in the circulation varies greatly from thirty-three to one hundred days and that the elimination is not a continuous process but occurs in "more or less cyclic crises," the responsibility for the disappearance of the transfused blood from the circulation apparently resting "more heavily on this cyclic activity of the body than upon the condition of the corpuscle." This blood-destroying activity is periodic both in men and women and in the latter is coincident with menstruation.

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**Study of Transfused Blood. II. Blood Destruction in Pernicious Anemia.**—From results of a study of 34 cases of pernicious anemia patients (Groups I, II and III) who received Group IV transfusion, ASHBY (*Jour. Exper. Med.*, 1921, xxxiv, 147), employing the same technic, was unable to realize the intensive blood destruction more generally assumed to be the important cause of the anemia. Of the 4 pernicious anemia patients who were studied until the elimination of transfused blood was complete, or almost complete, the curves compared well with the longest curve of elimination obtained in a normal person and were much longer than the other 7 completed curves obtained from individuals without blood disease. In contrast to the stability of transfused blood in pernicious anemia cases was the elimination which occurred in certain patients with other conditions—notably, hemolytic jaundice, aplastic anemia, myelogenous leukemia and carcinoma of kidney. The author states that the evidence presented shows "that there is no hemolytic toxin producing the anemia in pernicious anemia" and partial evidence showed "that the periods

of active blood destruction, which are seen as the exception in pernicious anemia cases during a series of transfusions, are due to the activity of the blood-destroying organs of the body rather than to the intrinsic weakness of the pernicious anemia blood corpuscle." That blood destruction is as important a factor in producing the anemia as it is at present usually assumed to be, is, in the writer's mind, questionable.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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BOSTON, MASSACHUSETTS,

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**Susceptibility of Rabbits to the Virus of Measles.**—GRUND (*Jour. Inf. Dis.*, xxx, 1922, xxx, 86) reports the results of an investigation to determine whether the inoculation of nasal secretions from patients with measles would produce definite and characteristic symptoms in rabbits. The majority of rabbits gave a certain reaction. In susceptible animals the incubation period varied between two and seven days. The least reliable and constant symptom was enanthem, which was present in about 20 per cent of the cases, although only 5 animals showed what one might describe as good typical Koplik spots. The temperature curve was not at all characteristic; in very few animals did the temperature go above 103° F. Conjunctivitis and inflammation of the upper respiratory passages, in varying degrees of severity, occurred in 70 per cent of the animals. Desquamation, either branny or flaky, occurred in all but 4 animals. Passage experiments from rabbit to rabbit were unsuccessful when nasal discharges were used, owing probably to the scantiness of the material. The writer states that it cannot be claimed that the results obtained in any one animal give a clear and typical picture of measles, yet taking the series as a whole, there has been enough conformity to encourage the belief that rabbits are susceptible to the virus of measles and within rather wide limits give a characteristic syndrome.

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**The Griffith Method for the Direct Isolation of Tubercle Bacilli.**—LYALL (*Am. Rev. Tuberc.* 1922, v, 899) has been able to isolate tubercle bacilli from 55 out of 56 specimens in pure culture from tuberculous sputum by the Griffith direct method. This method consists in mixing equal parts of sputum and 10 per cent antiformin, shaking or stirring in a test-tube, and a loopful of the mixture after it has become partly liquefied, streaked directly on to suitable media.

There is thus no sedimentation or washing which is ordinarily thought necessary to overcome the inhibitory effect of the antiformin. In this way, Griffith obtained cultures from 26 out of 31 specimens. The writer found that less than 5 per cent of a large number of tubes showed any contaminations. The most uniformly successful medium for the direct isolation of tubercle bacilli from sputum was one containing beef liver infusion in the proportion of 1 part of infusion to 4 parts of egg. The simplicity and uniformly successful results with this method constitute a distinct advance over other methods at present in use for the direct isolation of tubercle bacilli from sputum.

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**The Dissemination of Bacteria in the Upper Air Passages I. The Circulation of Foreign Particles in the Mouth.**—BLOOMFIELD (*Am. Rev. Tuberc.*, 1922, v, 903) states that his experiments were undertaken because previous bacteriological observations had indicated that microorganisms introduced into the mouth were rapidly removed, and that bacteria located in a focus, such as the tonsil, were not uniformly spread throughout the mouth cavity. It seemed likely, therefore, that there was some definite mechanism for promptly removing such foreign bacteria in an orderly way. The writer's experiments with foreign particles crudely duplicate what might be expected to obtain in the case of the deposition of bacteria. They show: (1) That such particles for the most part tend to be anchored in the protective mucous layer, and (2) that they are subsequently rapidly and directly removed by a series of suction currents. Obvious exceptions in regard to the speed of removal occur, owing to anatomical peculiarities and variations. The most significant finding, however, is in connection with the tonsils. It is generally believed that these structures were a collecting place for foreign bacteria which enter the mouth. The present experiments show that the tonsils are very well protected from contamination because of their situation behind the anterior pillars, and because of the course of the suction currents; but that when in some way foreign particles do lodge on them such particles remain stagnant for a considerable length of time. The writer, therefore, concludes that we have additional evidence of the protective mechanism which rids the mouth of foreign bacteria. That this mechanism frequently fails under unusual or abnormal conditions is obvious, but when one speculates on the degree of probable infection which would exist without it, it seems remarkably efficient.

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**Transmission of Tularemia by the Mouse Louse (*Polyplax Serratus*) (Burm).**—FRANCIS and LAKE (*Public Health Reports*, xxxvii, 83) summarize their work as follows: "The transmission of tularemia was effected in 12 out of 17 attempts through the agency of the mouse louse (*Polyplax serratus*) by the transfer of lice from white mice dead of tularemia to healthy white mice, the interval elapsing between infestation of the healthy mice and their deaths varying from five to twelve days—the average being seven and one-fourth days. The number of lice transferred in the 12 successful attempts varied from 12 to 43, the average being 25. The intervals which elapsed between the deaths of infected mice and the transfer of their lice to healthy mice varied from a few minutes to eighteen hours.

Transmission of tularemia by lice was thus effected to two series of mice, the first series being infected by lice removed from inoculated mice and the second series being infected by lice removed from the louse-infected mice of the first series. When inoculated mice were dropped into a jar in contact with lousy healthy mice the infection killed off all the healthy mice in twenty-five days. Transmission in this case was probably due to lice. Blood-sucking mites of the species *Liponyssus isabellinus* removed from an infected white mouse were crushed and injected subcutaneously into another white mouse, causing its death from tularemia. The urine of infected white mice was infective for guinea-pigs when injected subcutaneously into the latter. Similar urine failed to infect white mice when fed to them on corn meal. The mouse louse (*Polyplax serratus*) commonly found on our white mice was absent from 56 house mice caught in snap traps in the laboratory."

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**Transmission of Tularemia by the Bedbug (*Cimex Lectularius*).—**FRANCIS and LAKE (*Public Health Reports*, xxxvii, 83) have shown that bedbugs readily serve to transmit the infection of *B. tularensis* from mouse to mouse. The infection may be by biting but is more regularly brought about by allowing mice to eat the bedbugs. Bugs infected by biting infected mice were infective as long as one hundred days. The feces of infected bedbugs remained infective for mice as long as one hundred and twenty days.

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**Cultivation of Bacterium Tularensis on Mediums New to this Organism.**—FRANCIS (*Public Health Reports*, xxxvii, 102) reports the cultivation of *B. tularensis* on a variety of mediums other than egg yolk on which it was originally grown. This applies to original isolations as well as to subcultures. Egg yolk, however, is regarded as best adapted to routine use.

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**An Occupational Dermatoconiosis Among Zinc Oxide Workers.**—TURNER (*Public Health Reports*, xxxvi, 2727) mentions the frequency of skin diseases of occupational origin and describes a condition which is common among workers in zinc oxide and is known popularly as "oxide pox." The lesions result from clogging of sebaceous glands with the powder, and this is followed by infection. The eruption is an itching papular eruption with a white central plug, composed largely of zinc oxide. This is followed by an eczematous stage and finally some exfoliation. There are no general symptoms. Staphylococci were present in the lesions in nearly all cases. The disease is most common in the summer months and daily baths seem to prevent it.

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**The Nitrogen Requirement for Maintenance in Diabetes Mellitus.**—MARSH, NEWBURGH and HOLLY (*Arch. Int. Med.*, 1922, xxix, 97) estimated the nitrogen balance in 12 cases of diabetes mellitus, and determined a diet low in protein which would maintain nitrogen equilibrium. The cases varied in age from eighteen to eighty years and also in severity, but over one-half were of the more severe type. In spite of the fact that these diets (fully set forth in the case reports) cannot be considered as the lowest in which nitrogen balance could

have been established, they contained an average of 0.68 gm. protein per kilogram of body weight. The average number of calories per kilogram of body weight given to this group of patients was 33.5, and of these calories an average of only 3.8 per cent were in the form of carbohydrates. The average amount of foodstuffs used per kilogram of body weight was: protein, 0.68 gm.; fat, 3.28 gm.; carbohydrate, 0.32 gm. The authors discuss certain fundamental laws governing protein metabolism in normal individuals which they summarize as follows: "In mixed diets carbohydrate and fat are equally efficient in sparing protein and of equal value as fuel for work. Carbohydrate may not be entirely replaced by fat, however. An animal having a supply of body fat will burn the same amount of fat, whether it is supplied in his diet or is used from his store. A good supply of body fat thus saves protein in the same way as ingested fat. More nitrogen is excreted during the days following a diet rich in protein than following one poor in protein. The increased heat elimination, due to the metabolism of food, has been pointed out, and the excessive 'specific dynamic action' of protein has been emphasized. Work causes an increase in the total metabolism, but no increase in the protein metabolism provided the calories needed are supplied in other form. Children require more protein than adults, and the total requirement decreases as age advances. Sex is of no importance in studies of protein metabolism. There is a marked day-to-day fluctuation in nitrogen excretion, partially dependent on increased water intake. Changes in weight must be interpreted with caution, because they are often due to changes in the water content of the body. The infectious fevers cause a great increase in the amount of protein destruction." They then point out fallacies in the arguments used and data provided by previous writers to show that in diabetics the nitrogen requirements are higher than in normal individuals and offer their figures as proof of this point. They conclude: (1) "Nitrogen balance can be established in the diabetic according to the laws applicable to the normal subject provided his total caloric requirement can be satisfied. This implies that he can burn enough glucose to metabolize fat. Diabetics who cannot burn this small amount of glucose are extremely rare. (2) Protein metabolism above the minimal is undesirable in the diabetic because of (a) the great glyco-genic property and (b) the large specific dynamic action of protein. Excessive protein metabolism results from a diet containing either too much protein or too few total calories."

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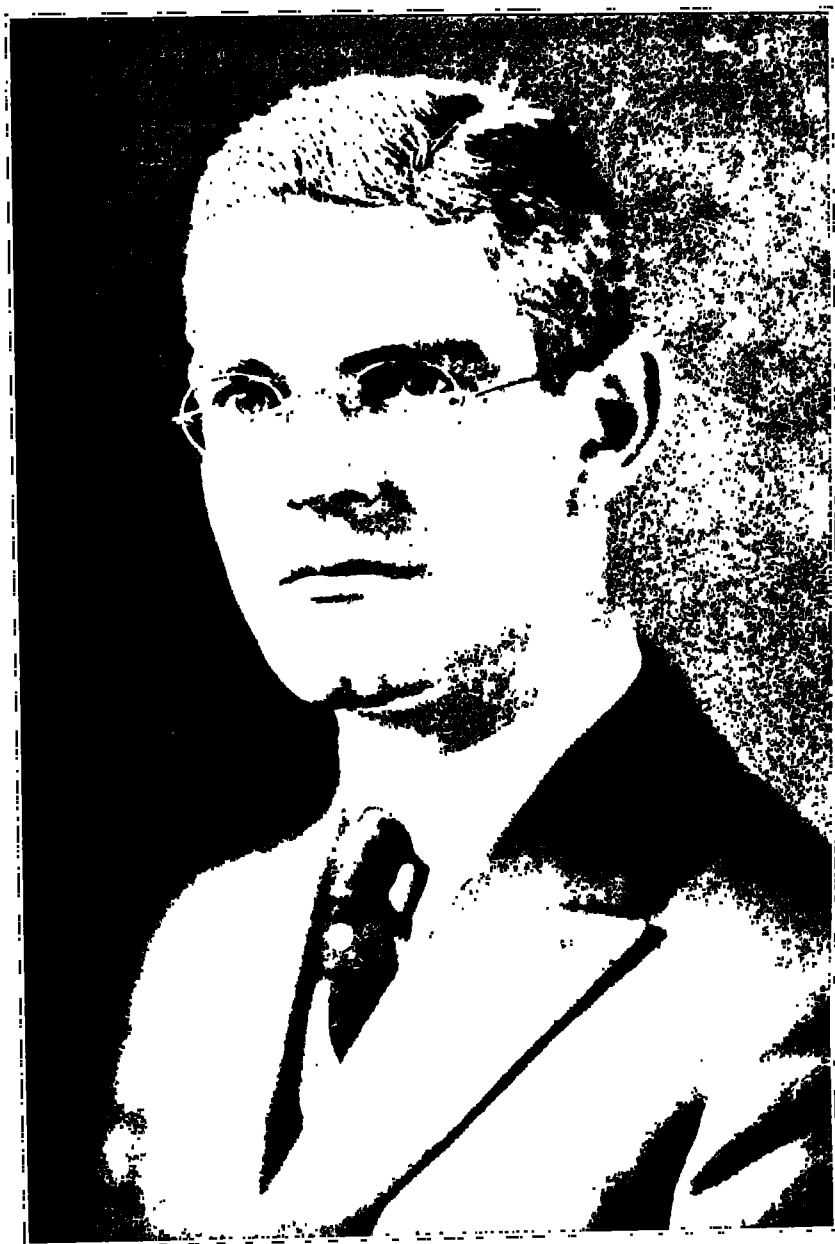
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*Geo. Morris Pierce*

## GEORGE MORRIS PIERSOL, M.D.

EDITOR OF THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

MAY, 1911—APRIL, 1922.

WITH the publication of the April number of the AMERICAN JOURNAL OF THE MEDICAL SCIENCES, Dr. George Morris Piersol resigned as editor, a position which he had held for eleven years. Dr. Piersol assumed the management of the JOURNAL when the death of the previous editor, Dr. A. O. J. Kelly, occurred in 1911. It was his constant endeavor to keep the JOURNAL on a high plane, as regards both the literary and scientific quality of its pages, and that he achieved success is evidenced by the high esteem in which the JOURNAL is held by the profession throughout the civilized world, and by a steady and continual growth in circulation, notwithstanding the increase in the number of very excellent periodicals devoted to special phases of medicine, in the last decade. Under Dr. Piersol's editorship the writings of the foremost men in all branches of medical science have appeared in its pages, many of these contributions marking epochs in medical progress, so that the AMERICAN JOURNAL OF THE MEDICAL SCIENCES is today one of the most widely and frequently quoted of all medical periodicals.

It is with sincere regret that his many friends see him relinquish the work which he has conducted so admirably for so many years. However, the activities of a very busy teaching life and an extensive consulting practice require his entire attention. At the present time he holds the position of Professor of Medicine and Sub-Dean in Medicine in the Graduate School of the University of Pennsylvania, and Professor of Medicine at the Woman's Medical College of Pennsylvania. Dr. Piersol has just completed his term of office as President of the Philadelphia County Medical Society, a position which he attained not only as a result of his medical achievements but also through the universal popularity with which he is greeted throughout the city by the medical profession. In addition to these honors he is a member of the Association of American Physicians, The American Therapeutic Society, American Climatological Association and other organizations national in their scope. During the war Dr. Piersol was in active service for nearly two years. In the A. E. F. he served as Chief of the Medical Service of U. S. A. Base Hospital No. 20, later as temporary commanding officer of the same organization and subsequently as corps consultant with the rank of Lieutenant-Colonel. Dr. Piersol has many years of activity before him and there can be no question that the future will be full of great possibilities for one of his ability and talent. The AMERICAN JOURNAL OF THE MEDICAL SCIENCES extends to Dr. Piersol its best wishes for a long and most successful career.



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ORIGINAL ARTICLES.

**IMPENDING AND REAL GANGRENE ASSOCIATED WITH DIABETES; CORRELATION OF MEDICAL AND SURGICAL EFFORT.**

BY BERTRAM M. BERNHEIM, M.D., F.A.C.S.

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It is well known that gangrene of the extremities is a fairly frequent complication in diabetes; not that the condition of diabetes itself necessarily gives rise to gangrene, but that in individuals suffering from this malady there is usually to be found an associated generalized arteriosclerosis which, together with the recognized lowered resistance of the tissues to infection, may be said to prepare the field for those circulatory disturbances of the extremities that eventuate in gangrene.

At the same time it must be admitted that fundamentally the diabetes controls the situation in so far that most of those who come to grief with gangrene are found either to have neglected the general condition or are sufferers from it in such intractable form that dietetic and therapeutic measures for its relief have been unavailing. At least this is so in my experience. It appears that the basic element dependent upon control of the diabetic condition is not so much a cessation of further development of the arteriosclerotic process in the extremity bloodvessels as it is a raised tissue resistance to infection and to the withstanding of the ischemia associated with occluded arteries; for in most cases that have come under my observation a halting of the arteriosclerotic process is of comparatively minor importance, since it has already proceeded to the point

of almost total occlusion of the main terminal bloodvessel.<sup>1</sup> This leaves the limb to get along as best it may, with such collateral vascular channels as might have developed coincident with the gradual occlusion of these main vessels. The crux of the situation must therefore lie in the ability of the tissues to survive with a greatly diminished blood nourishment, and it is this ability which seems to be influenced by the diabetes.

That this is true is proved, I think, by the fact that in gangrenes other than those associated with diabetes it suffices in general to consider and treat the local condition alone, and if one is able to reestablish the circulatory balance in a limb of precarious circulation, as is very frequently possible by means of rest, baths and gentle massage, the use of the electric vibrator and such other measures as one may employ in these difficult conditions<sup>2</sup> a successful issue may be expected. Not so in diabetes. Not once but many times have all my efforts to restore the circulatory balance gone to naught until the underlying condition could be brought under control. I refer particularly to those cases of *only impending* gangrene, cases which have not progressed to the stage of actual tissue death and where prompt measures might be expected to prevent it.

But in a way the same thing holds true for those who have an actual gangrene in that amputation will more than likely end disastrously, as is well known, unless at the time of operation the patient is sugar-free, and his acetone, diacetic acid, blood-sugar and carbonate findings have been brought into line. Or a better way of putting it would be to say that a patient's chances of surviving operation appear to be increased just in so far as his underlying diabetic malady is brought under control. It follows, therefore, that surgeons would do well to call to their aid physicians skilled in the treatment of this difficult disease, for it requires a special order of knowledge to deal with its various manifestations, a knowledge not usually possessed by surgeons.

This was forcibly brought home to me by a case (Mr. J. W.), which came under my care some years ago, of a man, aged sixty-eight years long a sufferer from diabetes, whose bloodvessels everywhere were of the pipe-stem variety. He had been under the constant supervision of Dr. E. J. Leopold, and in spite of occasional lapses had been carried along most successfully for a number of years, even to the point of surviving a desperate pneumonia. One winter, for some unaccountable reason, he became obsessed with the idea that he needed no further medical supervision. Being a hard

<sup>1</sup> That is the main vessels of the lower leg and foot. It often happens that pulsation is felt in the popliteal artery, but invariably it is found to be one-half or three-quarters occluded by the sclerotic process. So the volume of blood passing through it must be very small.

<sup>2</sup> *Pain in Threatened and Real Gangrene of the Extremities; Its Relief*, AM. JOUR. MED. SC., 1922, 163, 517.

drinker he indulged immoderately and totally neglected his usual dietary precautions—and with the inevitable result. When I saw him he had what looked to be a simple infection of his left great toe. Dr. Leopold was again in charge, but the patient's attitude was bad and his medical adviser was having poor success.

I started out with the usual conservative measures of rest and moist, warm boric dressings, but the tissue broke down in spite of them. I then provided adequate drainage, but the tissues seemed to have little resistance, and although there was no pain at all connected with the affected area, more destruction ensued, and it was not long before the terminal joint was invaded. Dr. Leopold thereupon redoubled his efforts. Rigorous diet was enforced under adequate supervision and everything possible was done to stave off what looked like a spreading infection with gangrene. Dr. J. M. T. Finney saw the patient in consultation and advised that he be put to sleep, the joint opened, thoroughly cleaned out and all sloughing material removed. It was with a hopeless feeling that his advice was followed.

Just before this was done it was noted that the sugar content of the patient's urine was decreasing. Coincident with this it was further observed that while the roentgen-ray showed definite bone destruction in the joint, the surrounding tissue appeared to be taking on renewed vitality and that the inflammatory area had ceased to spread. The operation was carried out under nitrous-oxide gas anesthesia. For a few days the whole foot looked precarious, but actual gangrene did not supervene. After a while the condition seemed to improve some as the general condition of the patient began to respond to treatment. Shortly thereafter the diabetic process yielded, and following this the toe healed. The patient lived a fairly active life for several years after this, finally succumbing to a second attack of pneumonia.

I cite this case because it is a most unusual one and is a striking example of successful coöperation of surgical and medical effort. The whole period of surgical treatment was most tedious, and consumed four months.

Another case, equally striking was that of an elderly man, Mr. H. H. (a patient of Dr. Samuel Wolman), who also had long been a sufferer from diabetes. Always a difficult patient, he would at times go on a veritable carbohydrate debauch, and it was at the conclusion of one of these, in the spring of 1920, that he began to have pain in his right leg. This grew worse steadily until it became so acute and constant that it was agonizing for him to walk. Sleep was out of the question.

When I saw him, some two or three weeks after the onset, there was already present a slight but none the less definite atrophy of the calf muscles of the affected leg. When the man was on his feet the veins of his right leg stood out like whip-cords while the entire

skin from the knee down assumed first a fiery red color, and then as he continued standing a purplish, ominous-looking dusky red. I have noticed this remarkable phenomenon many times in cases of threatened gangrene, and have been at a loss to explain it. The pain that accompanies it is excruciating. It looks as if the filled, tense veins would burst, and one cannot escape the feeling that the contained blood is surely obstructed in its outflow. Yet there is no obstruction demonstrable, for the moment the patient lies down the whole picture disappears, and if his leg is elevated a bit it assumes a pale, cadaveric appearance with great rapidity.

It looks rather as if at certain stages of a failing circulation in the extremities the innervation of the vessel walls becomes deranged to such extent that with the patient in the upright position there is a total loss of tone, with the resultant vein bulging with stagnant blood and the generalized phenomenon as noted.<sup>3</sup> This view is further supported by the fact that the affair may be purely temporary; as the circulatory balance is reëstablished by appropriate treatment the phenomenon becomes less and less pronounced; the pain on standing decreases, and finally the leg becomes normal in appearance both upon standing and lying down. In other words the vascular innervation once more becomes operative and the vessels regain their normal tone.

This is well illustrated by the story of the patient in question, as in my earlier statement that little can be accomplished without the physician's aid. I insisted immediately that Mr. H. remain in bed and be entirely off his feet. He was given the electric vibrator, hot and cold plunges to the foot and leg and such other measures as seemed indicated.<sup>4</sup> As the patient was in his own home the treatment was difficult and the dietary precautions nullified by his wilful excesses. His whole foot was exquisitely sensitive, and as the days progressed the picture as noted above became so exaggerated that finally I insisted that he go to the hospital for a final though, as it appeared, hopeless trial at saving the limb.

At the hospital the unexpected happened. Rigid dietary precautions were enforced, and within seventy-two hours the sugar in the urine began to clear while the man's whole aspect took on a different character. His blood sugar was 0.164 per cent. The electric vibrator, which is nothing but the gentlest form of massage, was carefully used, hot and cold plunges were regularly instituted every four hours, the leg was kept warm at all times, and in addition the patient was given a course of Ringer's solution.<sup>5</sup> It was not long before the pain began to subside. To make a long story short the whole picture cleared to such an extent that a few weeks later the

<sup>3</sup> I lay great stress upon this phenomenon in the diagnosis of threatened gangrene.

<sup>4</sup> Pain in Threatened and Real Gangrene of the Extremities, Its Relief, *AM. JOURN. MED. SC.*, 1922, 163, 517.

<sup>5</sup> *Loc. cit.*

patient was walking about as well as ever, and he has continued to do so.

Not all cases end so happily. Only too often it is not so much a question of saving the limb as the individual's life, for while diabetes itself is quite compatible with long life, diabetes plus a gangrenous limb is in all cases an extremely serious affair. Not that amputation is such a desperate ordeal in itself, but that any operative procedure of whatever magnitude is of serious import in the case of diabetes, the degree of seriousness depending for the most part apparently upon the state of carbohydrate metabolism derangement.

By way of illustration, I wish to cite three cases, each of which teaches a somewhat different lesson, though fundamentally all of them illustrate the close interrelation of surgery and medicine required for the proper handling of such cases.

The first is that of Mr. M. S., aged sixty years, a patient of Dr. T. B. Fletcher. Long a diabetic, he arrived in Baltimore from the South in a profound state of acidosis. Some two or three weeks previous he began to have a soreness in his right foot, for which his medical adviser prescribed hot-water bottles. Several superficial burns on the toes resulted, and after that the dorsum of the foot became red and inflamed, and reddish streaks made their appearance above the ankle. It was then that he came to Baltimore.

Upon his arrival, April 2, 1921, he was critically ill, vomiting frequently. His urine was loaded with sugar, 2+ per cent, and also with diacetic acid and acetone, ++++. His blood sugar was 0.25 per cent and his blood carbonate 39 vol. per cent.<sup>6</sup> His foot was obviously infected, and it seemed to have an accumulation of pus just under the skin of the dorsum, while two of his toes were already gangrenous. There was, however, no outspoken lymphangitis, and the patient's temperature was hardly elevated. So in view of his precarious general state, surgical intervention was postponed until medical measures at least could be gotten under way.

Within a few days the toxic symptoms began to subside, so that it was possible to incise and drain the dorsum of the foot. The operation was done under local anesthesia with the patient in his bed. Quantities of foul-smelling, grayish-black pus, such as is characteristically found in the tissue destruction of gangrene, were released. Following this the whole dorsum of the foot gradually became gangrenous and at each dressing that part which was obviously destroyed was removed. The two toes were removed in the same way, and as a third toe wilted it too was removed—piecemeal.

It was necessary to do this, I felt, because the accumulation of necrosed and sloughing material, with its accompanying foul-smelling liquefaction, was so great that to leave it meant that a certain amount of absorption of toxic matter must result. To have removed

<sup>6</sup> I am indebted to Dr. Louis Sacks, resident surgeon at the Hebrew Hospital, for much aid in the preparation of this article.

the foot—as was obviously indicated—was out of the question at this time, because the patient's general state remained so desperate as to preclude giving him an anesthetic or carrying out any operation of magnitude. But we were particularly fortunate in this case,<sup>7</sup> because the individual in question never suffered the slightest pain from his rapidly decaying foot. This was one of the most remarkable cases in this respect I have ever encountered. Thus by keeping well away from the line of demarcation, which was progressive, all excision of tissue was accomplished without pain and without anesthesia of any kind.

Under the constant watchfulness of Dr. Fitcher, Mr. S. gradually improved. His urine revealed less and less sugar until, weeks after his admission, it finally became sugar-free. His acetone and diacetic acid, however, were very refractory, being +++ for the acetone and + for the diacetic acid. It seemed impossible to get his blood sugar below 0.21 per cent, in spite of repeated starvation days and the most rigidly careful diet on other days.

During these trying weeks there was the widest possible opening in the foot for drainage, the skin, subcutaneous tissue, extensor muscles and tendons having been removed. But the interosseous muscles were becoming affected and sloughing material was constantly oozing up between the metatarsal bones. It then occurred to me that even though the patient's temperature was running about normal, absorption was going on nevertheless, and that this was the reason for the failure of urinary and blood findings to approach normal. Dr. Fitcher and I discussed this possibility and the proposition that as long as the affected leg remained unamputated the diabetic condition of the patient probably would not show further improvement. I must admit that, surgically speaking, the man's wounds were so wide open that absorption of any serious surgical significance seemed out of the question. My only ground for thinking that there was any absorption at all was merely the fact that the most intensive efforts of the medical men to improve the diabetic condition after it had reached a certain point were without avail. Our combined experience, however, in regard to this matter was rather meager, and the literature contains little or nothing concerning it.<sup>8</sup> It seemed a marvelous opportunity to shed some light on this point by proceeding with the amputation—and the temptation was great—but the patient's condition was such that it would have been unwise to carry out any operation without exhausting every possible means of bringing his laboratory (blood and urine) findings to normal. We therefore continued our

<sup>7</sup> The gangrenes of diabetes are more prone to be of the painless variety than other gangrenes, though just why this should be I do not know.

<sup>8</sup> Ordinarily, if a patient is absorbing from a surgical wound, one feels that the drainage is insufficient and that this will be manifested by pain, swelling and elevation of temperature.

efforts in this direction even though the gangrenous process continued to advance. I might add that the circulation in the affected leg was quite satisfactory, the patient had his normal femoral and popliteal pulses, and that such granulation tissue as formed bled with remarkable ease. In other words the spread of the gangrene was not dependent upon a circulatory failure but obviously upon a lowered resistance of the tissues to infection and to ischemia. Lest there might be some skepticism on this point, I would add that not only was the circulation quite satisfactory, but there was no edema of the foot, ankle or leg which might have interfered with a circulation that was adequate. But toward the seventh week under our care the sole of the foot began to redden. A little later it became obvious that the process had broken through the plantar fascia from above (as was to be expected), and if prompt measures were not taken a fulminating gangrene might result. This, of course, was to be avoided at all hazards. At this time the urinary and blood findings were as follows:

May 18, 1921. Urine: Glucose, 0.7 per cent (14.7 gm.); acetone, +++; diacetic, +; albumin, +. Blood sugar, 0.24 per cent.

That is they still had not reached normal. The opportunity to discover the relation of absorption from gangrenous tissue to continued carbohydrate derangement in so far as a single example could teach was within our grasp. We had played fair with the patient from an actual surgical standpoint by carrying him along without operation until his leg actually began to threaten his life.

Therefore, on May 19, 1921, under nitrous oxide gas and some ether, a hurried amputation was done at the midcalf. The patient reacted very well, and, with the exception of one small area on the outer side of the stump, the wound healed without difficulty. As we had hoped, the postoperative course of the diabetes justified fully the view held that the failure of the carbohydrate derangement to yield entirely to treatment was due purely to the absorption taking place. At least there is no other explanation for the fact that within about two weeks after the operation, June 14, 1921, the urinary findings came down to normal. The blood sugar dropped to 0.20 per cent and continued to decrease, reaching normal one week before discharge from the hospital, July 13, 1921, some three and a half months after his admission.

At this time he was on an extremely liberal diet. Daily diet the week of discharge from the hospital was as follows:

*Morning:* Lister biscuits, 2; peach, 1; eggs, 2; milk, 270 cc; coffee, 250 cc; butter, 10 gm.

*Afternoon:* Orange, 100 gm.; broth, 200 cc; beef, 100 gm.; squash, 150 gm.; tea, 200 cc; cucumber, 100 gm.; potato, 100 gm.; lister biscuit, 2. Ice cream: Milk, 150 cc; cream, 160 cc; saccharine,  $\frac{3}{4}$  gr.



*Evening* (supper): Cottage cheese, 50 gm.; beef, 100 gm.; squash, 150 gm.; tomato, 75 gm.; lettuce, 25 gm.; milk, 300 cc.; coffee, 250 cc; lister biscuits, 2.

His general condition was all that could be desired and his carbohydrate tolerance had actually been raised to really respectable limits.

This case, then, is an illustration of the principle that in certain instances our efforts must be directed not so much toward saving the limb as saving the patient's life, and that even this at times is most problematical.

For example, just recently I had under my care a woman (Mrs. K.), for many years a sufferer from diabetes, who began to have trouble with her right leg. She was seen by Dr. Helfgott, who advised that she come to the hospital for treatment. His advice was ignored and he lost sight of her for some three months. At the end of that time the patient again came under his observation, but by that time her whole right foot had become gangrenous.

I saw her in consultation April 8, 1921, and had her sent to the hospital immediately. The patient's whole foot was decayed, the toes were hanging by shreds of tissue and in several areas where the skin was broken great quantities of pus could be expressed from the sole of the foot. The gangrenous process was gradually spreading up the ankle and the lower leg was edematous. Her urinary and blood findings at this time were as follows:

*Urine:* Sugar, ++++; acetone, ++++; diacetic acid, +.

*Blood:* Blood sugar, 0.4 per cent; blood carbonate, 48.6 vol. per cent.

Dr. Leopold, the attending physician at the Hebrew Hospital, felt that if operation could be postponed a few days it might be possible to do much in the way of improving the patient's condition and rendering the operative outcome more certain. Accordingly the foot was dressed in wet boric compresses, and from day to day the gangrenous material was removed. This patient suffered so much pain at all times that it was difficult to do much with her. For some ten days this coöperative method of medical and surgical treatment was continued and the patient showed some favorable response. The findings were as follows:

*Urine:* Glucose, 0; acetone, ++; diacetic acid, +.

*Blood:* Blood sugar ranged from 0.396 per cent to 0.48 per cent.

At this time, however, the edema of the lower leg was becoming more pronounced. It spread up the leg and definite lymphangitic streaks made their appearance chiefly along the internal saphenous vein. In other words it became obvious that the infection was progressing and that the patient's life depended upon prompt surgical interference. Accordingly a mid thigh amputation was carried out. At the time of the operation the patient was in much better physical condition than upon her admission. Her tempera-

ture was down and she was practically sugar-free. Dr. Leopold and I felt that she would do fairly well after the operation, but we were disappointed. During the first twenty-four hours she was in desperate shape, but by the use of intravenous sodium bicarbonate she was tided over. For three days thereafter, April 23, 1921, she was showing improvement, and we began to feel hopeful. Her blood sugar dropped from 0.48 per cent to 0.34 per cent. Then with but little warning, some twenty-four hours after this, the patient suddenly went into a coma and died.

This case is an illustration of the difficulties that may be encountered at any time in the treatment of gangrene, namely, that a gangrene which is quiescent may suddenly become fulminating no matter what the condition of the patient. Under these circumstances, of course, operation is the lesser of two evils, and the patient must take the chance.

In the case of a third patient, Mr. S., aged fifty-four years, the conditions were even more deplorable. Not only was there the diabetic condition with a fulminating gangrene of the leg present, but in addition there was active pulmonary tuberculosis of long standing with cavities in both lungs. This involved state of affairs existed when I first saw the individual, the case having been treated on the outside for several months by others. Dr. Charles Austrian was invited to take over the medical side of the case, and at his suggestion a midthigh amputation was carried out under spinal anesthesia. The operation was done as an emergency at night; such was the danger from the rapidly advancing gangrene.

The patient was a large, fat, flabby man, definitely toxic. He had been under a fairly rigid diabetic regimen for some time at home, and as a result his urine was practically normal on admission. His blood sugar was 0.25 per cent and blood carbonate 33 vol. per cent. Despite the unfavorable outlook (to our surprise and relief) he stood the operation unusually well. With the exception of an annoying hiccup, that persisted for about forty-eight hours, his convalescence was uninterrupted. His carbohydrate metabolism was rapidly controlled, with the result that prior to his discharge from the hospital his diet was almost as liberal as that of a normal individual; his urine was sugar—, acetone—, and diacetic acid-free; his blood sugar was 0.117 per cent and blood carbonate 45 vol. per cent. His carbohydrate tolerance had been raised to really respectable proportions.

These various cases are illustrations of what may be accomplished by closely allied medical and surgical forces when arrayed against a really dangerous condition. I have taken particular pains to emphasize this feature because it has been my experience that physicians tend to handle the surgical complications of diabetes too much by themselves, thereby frequently losing the opportunity for constructive measures. This is the one side. On the other

side I find that the surgeon, when once he is consulted, is too prone to disregard the medical phase of the situation in his efforts to overcome the surgical complaint. How much better it would be for all concerned if there were an intelligent coördination of effort from the very start.

## THE PREVENTION OF SIMPLE GOITER IN MAN.<sup>1</sup>

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To understand why anyone should undertake a goiter survey of a whole community for the purpose of establishing a principle of prevention by a simple and practical method, it is necessary to study the literature of goiter with this idea in view. For the literature, while rich in statements regarding the distribution of goiter, the pathology of the thyroid gland, methods of medical and surgical treatment, hereditary tendencies and etiology, has little indeed to offer regarding the *prevention* of goiter.

A survey for merely determining the incidence of goiter in the different localities and cities of this portion of the Great Lakes basin would have been unnecessary. There is an abundance of scientific data giving in general the geographic distribution of endemic goiter throughout the world. Surveys of various communities in Europe have been made and the scientific data of the last century has so emphasized the sociologic and economic importance of endemic goiter, cretinism and deaf-mutism that national commissions have been appointed by some of the countries of Europe to study this problem for the purpose of finding some method of relief.

For ten years preceding the beginning of our work in Akron, Marine and Lenhart, working in the department of experimental medicine of the Western Reserve University, had been showing the ease with which endemic goiter could be prevented. The results of laboratory experiments and demonstration in animals, however convincing, must be applied to man for final proof of their prophylactic or therapeutic value. The prevention of goiter in man was yet to be proven. Therefore, with Dr. David Marine, I undertook to establish in man the applicability of the work of Marine and Lenhart as summed up in their statement that "simple goiter is the easiest of all known diseases to prevent."

**Definition and History of Endemic Goiter.** The term goiter means hypertrophy of the thyroid gland. The term as used in this paper refers only to what is known as *simple* or *endemic goiter* and does not include the so-called exophthalmic goiter.

<sup>1</sup> Presented as a thesis for the degree of Master of Arts in Medicine, Western Reserve University, June, 1921.

The incidence of simple goiter is so high and so continuous for generations, in certain districts of the world where all kinds of domestic animals as well as humans are involved, that it has come to be considered as characteristic of or endemic in that district.

The study of the history of this disease is like studying the history of the human race. The Arthorva Veda, an ancient Hindu collection of incantations dating from 2000 B. C., contains extensive forms of exorcisms for goiter. Caesar mentions the frequent occurrence of big neck as one of the peculiar characteristics of the Gauls. The origin of the term cretin shows the familiarity of the early Romans with this disease. They originated this expression of contempt by calling the myxedematous idiots Christians. The Swiss physician Paracelsus (1493-1541) was the first to emphasize the relationship between goiter and cretinism, and the earliest positive information concerning the latter disease dates from this author. In 1793 appeared Fodere's essay on "Goiter and Cretinism in the Maurienne and Aosta Valley," and in 1800 his *Treatise on Goiter and Cretinism*. During the last century there have been numerous publications on endemic goiter and cretinism, one of the most exhaustive of which is by A. Hirsch, in his study of the *Historical and Geographical Relations of Goiter*.

About the middle of the last century the governments of the European countries began to see the economic and sociologic importance of this problem. In 1848 the Sardinian government appointed a commission to study the cause of endemic goiter and find some method of relief. In 1864 the French government appointed a similar commission, which reported in 1874 that at least 500,000 people in France were suffering from goiter and that there were over 120,000 cretins and cretinoid idiots. This commission seemed to establish as a scientific fact the popular idea that goiter is a water-borne disease. In 1908 Switzerland created a goiter commission, and since then Italy has created a similar commission to study the cause and prevention of endemic goiter.

**Distribution.** The extent to which goiter prevails throughout the world is seldom appreciated. Few countries are free from endemic districts, and we find the so-called sporadic cases of goiter in every section and among every nationality in the world. But there are localities in which the incidence of goiter is so extremely high that they have been known for years as endemic goiter districts. The best known of these districts is in southern Europe, or, more specifically, the Alps mountain region, comprising southeastern France, southern Germany, all of Switzerland, northern Italy and southern Austria. In Asia practically all of the Himalaya district is an endemic goiter belt, with a very high incidence in northern India and parts of southern and western China and eastern Mongolia. In South America goiter is endemic throughout most of the Andes region, with probably the highest incidence of both goiter and

cretinism on the Peruvian plateau and in parts of western Brazil. In North America goiter is endemic in the whole of the Great Lakes' basin, in the basin of the St. Lawrence and in the northwest Pacific region.

In each of these large endemic regions there are localities in which the incidence of goiter is much higher than in the surrounding territory, and in such districts all of the domestic animals are affected. In some of these smaller districts the incidence of goiter has been determined with sufficient accuracy to be mentioned here. For example, as we have stated above, in 1874 the Goiter Commission of France estimated that in that country there were 500,000 goitrous people and 120,000 cretins and cretinoid idiots; statistics furnished by Kocher show that 80 to 90 per cent of the school children of Berne were goitrous; in his recent reports Klinger states that in some of the schools of Zurich, where he is carrying out methods of goiter prevention, 100 per cent of the children are goitrous. In southern Bavaria, according to the statistics of Schittenhelm and Weichardt, who base their conclusions on examinations of school children, the incidence of goiter is as high as from 77 to 89 per cent of the total population. In Switzerland and in certain provinces of Italy, France and Austria the problem of endemic goiter, cretinism and deaf-mutism has been recognized as of sufficient economic importance to demand investigation by their respective governments.

We are told that on the Gobi Desert and the plateau of Thibet the incidence of goiter is very high, and that among the various tribes of southeastern Mongolia a third of the population is goitrous.

McCarrison carried out some of his researches and made several surveys in Himalayan India. He states that in some of the villages of this section it is difficult to find a man, woman or child who is not suffering from the deformity. He estimates that not less than 20 per cent of the total population of Gilget, in northern India, suffer from goiter, and that among a population of 70,000 he found 200 cretins.

The frequency of goiter in North America has been known in a general way for more than a century. In 1800 Barton wrote an excellent monograph on the occurrence of goiter among the American Indians living along the shores of Lakes Ontario and Erie. Other goiter centers among the Indians of the Rocky Mountain States have been described by Munson. Adami pointed out the frequency of goiter in the St. Lawrence Valley, and speaks of French Canadian villages in this district in which there was scarcely a family without one or more goitrous members. Osler has emphasized the frequency of goiter in Ontario. Marine finds the disease widely disseminated all along the Great Lakes, where it occurs not only in humans but also in animals, especially dogs and sheep. In a report to the Commission of Conservation of Canada in 1918,

Shepherd states that the incidence of goiter is very high in British Columbia and Alberta, and that in some localities of these large states most of the domestic animals are affected.

**Incidence of Goiter in the United States.** Efforts to determine the incidence of goiter in different sections of the United States have been made but no accurate survey of a whole community had been reported previous to our work in Akron. In 1913 Clark examined 13,836 school children in eleven counties of West Virginia and found 1234 cases of goiter—9 per cent of the number examined. In Virginia the same worker examined 6432 school children and found 817 cases of goiter, or 12 per cent of the number examined. In Huntington 50 per cent of the girl students were found to be affected. In the Virginia survey less than 0.1 per cent of the goiters found were among boys.

The report of Hall of 3339 students at the University of Washington is indicative of the incidence of goiter in the Northwestern States. This writer found enlarged thyroids in 18 per cent of 2086 men whose average age was twenty years and five months, and in 31 per cent of the 1253 women examined whose average age was nineteen years and three months.

In Chicago, Olson examined 606 women and 193 men, with ages ranging from eighteen to sixty years. Among the women 18 per cent had well-developed goiters, and 7 per cent of the men were affected.

During 1917 and 1918, when so many of our young men were in camp, an opportunity was offered to determine the incidence of goiter among young men and to compare the incidence of goiter in different sections of the country. Thus from Camp Lewis, Washington, Kerr reported the examination of 21,182 recruits, with the finding of 1276 large or well-formed goiters. The percentage of unquestionable goiters compared to the number of recruits from each state was as follows:

Washington, 11 per cent.

Oregon, 8.6 per cent.

Idaho, 7.3 per cent.

North Dakota, 6.6 per cent.

Utah, 5.5 per cent.

Minnesota, 5.1 per cent.

Wyoming, 3.7 per cent.

South Dakota, 2 per cent.

Nevada, 1.1 per cent.

Colorado, 0.5 per cent.

Brendel and Helm, studying the same problem at Camp McDowell, California, conclude that goiter is endemic in Washington and Oregon. Smith, at Jefferson Barracks, Missouri, reports that in the examination of 65,507 men there were found 1074 cases of simple goiter, or an incidence of 1.63 per cent of the total number

examined. These recruits represented fifteen different central and western states. These findings only emphasize in a general way the fact that goiter may be considered as distinctly endemic in certain sections of the United States.

**The Physiology of the Thyroid.** In order to appreciate the principle of goiter prevention one must review briefly the biochemistry and function of the thyroid gland.

Early in the sixteenth century Paracelsus emphasized the relation between endemic goiter and cretinism. In 1825 Parry's descriptions of cases of goiter or enlargement of the thyroid gland in connection with enlargement of the heart with palpitation and exophthalmos were published. In 1835 appeared Graves's description of the clinical complex of exophthalmic goiter, with enlargement of the thyroid as one of the cardinal symptoms. Basedow's description of the same syndrome appeared in 1840. But none of these observers interpreted their findings in terms of the function of the thyroid. The first important observations of the functions of the thyroid were published in 1874 by Sir William Gull. At this time the clinical complex of myxedema (Gull's disease) was described in detail, and this clinical picture was interpreted as in some way associated with a lack of function of the thyroid.

Gull's observations and interpretation of the etiology of myxedema were confirmed in 1880 and 1881 by Kocher and Reverdin, who had observed the results of the total removal of goitrous thyroids. Kocher gave to the clinical syndrome resulting from complete thyroidectomy the name of cachexia strumipriva. Reverdin called it operative myxedema. In 1877 Ord designated the disease as myxedema, because he thought he had recognized a mucoid change in the subcutaneous tissue. Sir Victor Horsley verified the findings of these observers by his researches on experimental myxedema in monkeys. As a result of these observations, Murray and McKenzie in 1891 gave glycerinated thyroid extract to a myxedematous patient and obtained definite therapeutic results. Magnus-Levy, in 1895, showed that heat production was markedly reduced in cases of myxedema and that thyroid feeding raised it, thus establishing the essential or at least the major function of the thyroid as we know it today.

The early Greeks treated goiter by the internal administration of the ash of burned sea-sponges, not knowing that the substance was rich in iodides. Iodin was first knowingly used in the treatment of goiter by Coindet in 1820. From that time iodine was used very extensively and stood alone in goiter therapy for seventy-five years before the discovery by Baumann, in 1895, that iodine was a normal constituent of the thyroid gland. Our knowledge of the chemistry of the thyroid progressed rapidly after Baumann's discovery. In 1901 Oswald showed that the iodine is bound with the globulin and is contained for the most part in the colloid,

In 1907 Marine emphasized the fact that iodine is necessary for the normal function of the thyroid, and also in active hyperplasia of the thyroid the iodine store is reduced. The later experiments of Marine and Lenhart have established the following facts relative to the importance of iodine in the chemistry, function and histologic anatomy of the thyroid:

1. Iodine is a constituent of the normal thyroid of all animals with the ductless thyroid. As shown by their experiments on the rapidity of absorption of iodine by the thyroid, its elaboration into the active hormone and by alkaline hydrolysis, as introduced by Kendall, iodine exists in the thyroid in an *active* and *inactive* form. That is, the elaboration of the hormone goes on slowly from the inactive iodine collected from the blood. The excess of physiologically active iodine is for the most part stored in the "colloid" or globulin of the alveoli, and it is believed that colloid serves merely as the vehicle or means of storing the excess of this remarkably active substance in a harmless manner. The store of iodine then normally consists of inactive iodine for the most part in the cells and of active iodine for the most part in the colloid or thyroglobulin.

2. This store of iodine shows wide variations in any series of animals. These variations reach their maximum in the so-called goiter districts and their minimum in non-goitrous districts.

3. Further, these variations in iodine store have been shown to have an intimate relation with the histology of the gland. Thus in all species of animals with the ductless thyroid the iodine store is decreased in the hyperplasias. This decrease is proportional to the degree of hyperplasia. In mammals, *e. g.*, dog, sheep, ox, pig, rabbit, cat and man, it has been shown that normal thyroids have the highest percentage of iodine, averaging 0.2 per cent, with extremes of 0.1 and 0.5 per cent.

4. It has been further shown that as soon as the store of iodine falls below 0.1 per cent active hypertrophic and hyperplastic changes in the thyroid begin. In other words, no functional hyperplasia and therefore no goiter can develop, at least in the mammals above mentioned, if the iodine store in their thyroids is maintained above 0.1 per cent.

5. This iodine store may be rapidly and markedly increased by the administration of exceedingly small quantities of iodine in any known form and through a great variety of means, as inhalation, enteral and parenteral administration, cutaneous application, etc., and as indicated above, marked histologic changes are at the same time brought about in hyperplastic glands, namely, the arrest of the hypertrophy and the involution or return of the thyroid cells to their resting form.

The active iodine compound found in the thyroid, beginning with its discovery by Baumann in 1896, and the successive attempts to isolate it, has been known as iodothyron, iodo-thyro-globulin



(Baumann and Roos), thyroidin (Oswald) and thyroxin (Kendall). In 1915 Kendall succeeded in isolating this iodine-containing hormone in crystalline form and has determined its structural formula. He believes it to be tri-iodo-indol-propionic acid.

In 1895 Magnus-Levy indicated that the thyroid, in some way, controlled the rate of oxidation in the tissues. He showed that in myxedema the rate of metabolism was much lowered and that by feeding thyroid the rate could be raised. Also, he was the first to demonstrate that as regards metabolism exophthalmic goiter was the opposite to myxedema. This work has been confirmed from many sources as regards experimental and spontaneous myxedema. And as regards exophthalmic goiter, it has so developed that at present the rate of metabolism is the best available basis for classification.

In a recent publication on *The Physiology of the Thyroid*, Marine states that "The thyroid has to do in some important way with internal respiration or the utilization of oxygen by the tissues. Indeed, this is the only known function of the thyroid."

**The Prevention of Goiter.** Before 1896 Halsted had shown that if a portion of the thyroid is removed or destroyed the remainder undergoes hyperplasia. Marine and Lenhart found that this compensating hyperplasia could be prevented if the remainder of the thyroid was kept saturated with iodine. This was true in dogs as long as at least one-sixth of the gland was left, but if more than five-sixths were removed a compensatory hyperplasia followed even though iodine was given. This important observation pointed directly to iodine as the means for the prevention of thyroid hyperplasia (goiter).

One of the first practical applications of the principle of prevention of goiter and myxedema accidentally followed the discovery of salt in Michigan and its more extensive use (as crude salt) in the sheep industry of this state at a time when the industry was being crippled by endemic goiter. This crude salt was afterward found to be rich in iodine. The first definite application of the use of iodine in the prevention of goiter on a large scale in animals was the prevention of goiter in brook trout. This disease had been the cause of much trouble and expense. The so-called thyroid carcinoma in brook trout had become so serious at many private, state and government hatcheries that the question of abandoning the industry was being discussed. An investigation of the causation and a study of methods of prevention was undertaken by Marine and Lenhart in conjunction with the Pennsylvania State Fish Commission during the years 1909, 1910 and 1911. Their conclusions as to the etiologic factors producing goiter and the practical method of its prevention were definite and convincing. The important factors which in this instance caused endemic goiter were (1) overfeeding with an artificial food and (2) overcrowding. These investigators showed that goiter

could be prevented in young fish under the same environmental conditions which produced goiter by adding a very small amount of iodine to the food or water, or it could be prevented by changing the diet and remedying the overcrowding. The results of this practical research have been far reaching.

In addition to the experimental work above mentioned the treatment of goiter with iodine at the dispensary at Lakeside Hospital had been followed for the past ten years. Also the maternity dispensary of Lakeside Hospital had not only been using iodine in the treatment of goiter but had been using it as a prophylactic measure during pregnancy. To most of the men in touch with the goiter clinic at Lakeside or the school of medicine the prevention of goiter was no longer an experiment but an accomplished fact.

Therefore at the beginning of our work in Akron the possibility of goiter prevention had been clearly demonstrated by animal experimentation, but only a very limited application of methods of prevention had been made in man. No subject in preventive medicine had a sounder or more scientific basis for its practical application to man on a large scale than the prevention of endemic goiter. Yet there was considerable criticism and opposition which had to be overcome. This criticism centered about the possible untoward effects of iodine, especially the dangers of producing exophthalmic goiter.

**Etiology of Endemic Goiter.** Before anyone can fully comprehend the fundamental principles underlying the method of prevention which we have used, he must have some conception of the factors causing the disease. There have been many theories as to the cause of goiter, most of which are only of historic value and will not be taken up here. At present there are a few who consider goiter as a primary disease or idiopathic enlargement of the thyroid gland.

McCarrison considers it a water-borne infectious disease, the exciting factor of which is a *contagium vivum*, and suggests that it belongs to the colon group of bacteria. Shepherd, also, in his report in 1918 on the occurrence of goiter in Canada, concludes that it is a water-borne infectious disease, directly comparable to typhoid.

However, most of the scientific investigators of this country look upon goiter as a deficiency disease. Marine has been emphasizing this point since 1907. As has been pointed out:

1. Iodine is essential to the normal thyroid activity.
2. From a purely biochemical standpoint any substitution for iodine destroys the physiologic activity of the thyroid hormone.
3. From the histologic point of view glandular hyperplasia of the thyroid is due to a deficiency of iodine.
4. The physiologic action produced by thyroid extract is always proportional to the iodine content.
5. In animal experimentation if the iodine content is maintained

at or above one tenth of 1 per cent no anatomic changes toward goiter formation can take place.

These facts, with our results in preventing goiter in school girls by simply keeping the thyroid saturated with iodine, make the infectious theory at once untenable. These facts lead to the conclusion that the immediate or exciting cause of endemic goiter (hypertrophy of the thyroid gland) is a lack of iodine in the organism. This lack of iodine may be relative or absolute. The remote or fundamental cause of goiter is quite unknown.

**Practical Application of the Principle of Goiter Prevention.** In the practical application of the principle of prevention we chose the public schools for two reasons: (a) The children are in the adolescent age, the most important period in the development of goiter; (b) the public school group furnishes the best census of goiter in any community and makes it possible to carry out, through the school organization, the most expedient, economic and practical plan of prophylaxis and education.

In October, 1916, we explained the principle of the prevention of goiter to the superintendent of schools of Akron, Dr. H. V. Hotchkiss. He promised the full support of all the school authorities if the local medical society would sanction the work. After this idea had been explained to the Summit County Medical Association this body, in a regular session, voted to send the following message to the school board: "The idea of prevention of goiter as outlined can do no harm and may do good. We are in favor of seeing it carried out." The school board authorized the superintendent to call upon Dr. Marine and myself to make a survey of goiter among the school children of Akron and carry out any plan of prevention we saw fit.

In April, 1917, an examination for thyroid enlargement was made of all the girls from the fifth to the twelfth grades inclusive. The boys were not examined because of the relative infrequency of goiter in boys. The result of each examination was recorded on a special individual card, which on one side had space for the pupil's name, school, age, grade and the tabulations of four thyroid examinations. On the back of this card was space for the record of eight series of prophylactic treatments, which were recorded by the teacher giving the treatment. This goiter card was attached to the school record of each pupil and was transferred with the pupil whenever transfer to another school was made. In no other way could we have kept track of so many cases over so long a time.

The details regarding this examination and the plan for carrying out the treatment were then published. Only the resultant figures will be given here. 3872 girls were examined, with the following results:

Normal thyroids, 1688, or 43.6 per cent.

Slightly enlarged thyroids, 1931, or 49.9 per cent.

Moderately enlarged thyroids, 246, or 6.3 per cent.

Markedly enlarge thyroids, 7, or 0.2 per cent.

Among these there were 39 adenomas, or 1 per cent.

In April, 1917, the first prophylactic treatment was administered to more than 1000 girls who had elected to take it. No girl was urged and no one was permitted to take it unless she had a written permit from a parent.

In November, 1917, a second examination of all girls from the fifth to twelfth grades inclusive was made, in all 4415 cases, 1772 of which were new records. Of the 2643 old records 764 had taken the prophylaxis during the preceding six months and 1879 had not. As was published then there was not a single case in which a normal thyroid increased if the pupil was taking iodine, while among those not taking iodine 26 per cent of those marked normal at the first examination showed definite enlargement—some already having developed moderately large goiters. Even more than a prophylactic action was shown by the results—just one-third of the "small goiters" had disappeared and one-third of the "moderate goiters" had decreased 2 cm. or more.

In November, 1918, a third examination of 4277 girls was made. In October, 1919, 5520 individual examinations were recorded, and during the entire period 9967 different girls were reported.

**Effect of Prophylactic Treatment.** The prophylactic treatment as carried out for the past three years in the Akron schools consists of the administration of 2 gm. of sodium iodide, given in 0.2 gm. doses daily for ten consecutive school days, repeated each spring and autumn. The general data of the pupils not taking the treatment are given in Table I, and of those taking the treatment in Table II. Only pupils who have had two or more consecutive examinations have been included in these tabulations. A considerable number of pupils, both of those who have been taking the treatment and of those who have not been taking the treatment, have been omitted because they missed one examination, although otherwise their records were complete; 2305 pupils are included in the tabulation of those not taking treatment and 2190 in the tabulation of those taking treatment.

Furthermore, properly to interpret the results, it was necessary to take into consideration the length of time each pupil had been under observation. As the prophylactic treatment was given at intervals of six months we have used this interval as the unit and grouped the pupils according to the periods each had been under observation, *i. e.*, six, twelve, eighteen, twenty-four or thirty months. The results of only three groups, those with normal, slightly enlarged and moderately enlarged thyroids, are included because the fourth group, those with markedly enlarged thyroids, is too small. A comparison of the two tables brings out striking differences between those not taking and those taking iodine. These differences are

manifested both in *prevention of enlargement*—prophylactic effect—and in a *decrease* in the size of existing enlargements—therapeutic effect.

TABLE I.—RECORD OF PUPILS NOT TAKING PROPHYLACTIC TREATMENT.

Time under observation, mos.	Normal.				Slightly enlarged.						Moderately enlarged.					
	Unaltered.		Increased.		Unaltered.		Increased.		Decreased.		Unaltered.		Increased.		Decreased.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
6	47	50.0	47	50.0	93	69.4	36	26.9	5	3.7	16	69.6	7	30.4		
12	420	75.5	136	24.5	251	70.3	35	9.8	71	19.9	17	65.4	8	30.8	1	3.8
18	103	65.2	55	34.8	108	74.5	18	12.3	19	13.1	11	57.9	3	15.8	5	26.3
24	135	76.7	41	23.3	106	79.7	8	6.0	19	14.3	9	60.0	3	20.0	3	20.0
30	205	75.1	68	24.9	140	73.7	30	15.8	20	10.5	4	66.7	0	....	2	33.3

TABLE II.—RECORD OF PUPILS TAKING PROPHYLACTIC TREATMENT.

Time under observation, mos.	Normal.				Slightly enlarged.						Moderately enlarged.					
	Unaltered.		Increased.		Unaltered.		Increased.		Decreased.		Unaltered.		Increased.		Decreased.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
6	17	94.4	1	5.6	54	69.2	1	1.3	23	29.5	9	81.8	...	...	2	18.2
12	344	99.7	1	0.3	187	45.5	...	...	224	54.5	10	23.8	...	...	32	76.2
18	73	100.0	...	...	72	52.3	1	0.7	64	46.7	7	28.0	...	...	18	72.0
24	184	100.0	...	...	72	37.9	1	0.5	117	61.6	2	7.7	...	...	24	92.3
30	288	100.0	...	...	92	28.5	...	...	231	71.5	1	2.6	...	...	38	97.4

TABLE III.—SUMMARY OF RECORDS OF PUPILS TAKING AND NOT TAKING PROPHYLACTIC TREATMENT.

		Taking.		Not taking.	
		Totals.	Per cent.	Totals.	Per cent.
Normal:					
Unchanged	. . . . .	906	99.8	910	72.4
Increased	. . . . .	2	0.2	347	27.6
Slightly enlarged:					
Unchanged	. . . . .	477	41.9	698	72.8
Increased	. . . . .	3	0.3	127	13.3
Decreased	. . . . .	659	57.8	134	13.9
Moderately enlarged:					
Unchanged	. . . . .	29	20.3	57	64.0
Increased	. . . . .	...	...	21	23.6
Decreased	. . . . .	114	79.7	11	12.4
Total		2190	..	2305	

**Prevention.** The preventive value of the treatment is shown in the column marked "unchanged" and "increased." Taking the totals for the periods of six months each the following results were obtained. Of those that were normal at the first examination and did not take iodine, 347, or 27.6 per cent, had enlarged thyroids, while of those that were normal at the first examination and took iodine as outlined, 2, or 0.2 per cent, had enlarged thyroids. These two instances of enlargement were investigated.

The first pupil, aged sixteen years, had her thyroid examined and classified as normal on May 2, 1917, October 17, 1918, and December 3, 1918. At the examination on October 15, 1919, it was classified as slightly enlarged. This girl had taken 2 gm. of sodium iodide during each of the five possible periods, May, 1917, November, 1917, May, 1918, December, 1918 and May, 1919. A special examination was made on January 13, 1920, when the enlargement of the thyroid was verified. That this enlargement was acquired rather than congenital was shown by the absence of a pyramidal process of the thyroglossal tract. The tonsils were markedly enlarged and abnormally hyperemic. On direct questioning we were informed that the pupil was subject to recurrent attacks of tonsillitis. There was also slight enlargement of the lymphoid tissue at the base of the tongue and in the nasopharynx, and the general impression was that of a neurotic individual with general lymphoid hyperplasia.

The second girl, aged fifteen years, had her thyroid first examined and classified as normal on November 27, 1918. At the examination on October 16, 1919, it was classified as slightly enlarged. This girl had taken 2 gm. sodium iodide during each of the two available periods, November, 1918, and May, 1919. A special examination was made January 13, 1920, when the thyroid enlargement was verified. Careful inspection revealed the presence of Hutchinson teeth, depressed nasal arch and interstitial keratitis. We considered the case as one of neglected congenital syphilis.

Of the cases classed as having slightly enlarged thyroids at the first examination and *not taking* the prescribed iodine, 127, or 13.3 per cent, underwent further enlargement, while among those *taking* the prescribed treatment only 3, or 0.3 per cent, underwent further enlargement. Two of these 3 were reexamined on January 13, 1920, and the previous finding verified. One of these was another case of chronic infection of the tonsils with recurrent attacks of tonsillitis during the last year. In the second girl superficial inspection failed to show any pathologic condition to account for the enlargement. The third girl was not present for examination. These 5 cases were the only instances that showed enlargement of the thyroid out of 2190 pupils. Of the 2305 cases *not taking* iodine, 495 showed thyroid enlargement. Of the group with small goiters *taking* iodine, 659, or 57.8 per cent, returned to normal, while of the same group *not taking* iodine at school, 134, or 13.9 per cent,

returned to normal. However, we know that there is an error in the last figure, for many cases not taking iodine under the school jurisdiction were taking it in some form from their physician. No attempt has been made to detect or estimate this error.

In the practical application of the preventive treatment one must keep in mind the three periods when simple thyroid enlargements most commonly occur, namely, (a) fetal period; (b) adolescence; (c) pregnancy.

(a) The prevention of goiter in the mother and the fetus is as simple as the prevention of goiter which develops during adolescence. Practically it would seem that the prevention of goiter during these periods, *i. e.*, (a) and (c) is properly the responsibility of individual members of the medical profession supplemented by education of the public.

(b) The prevention of goiter in the adolescent period, on the other hand, should be a public health measure under state, county or municipal control. The existing systems of organization of the schools, both public and private, are sufficient to handle all the details without additional aid or expense. Education of the pupils could be combined with the actual administration of iodine, so that after leaving school they could continue the treatment if necessary. In industrial medicine physicians could render an important service in this direction. As thyroid enlargement is approximately six times as frequent in girls as in boys, each community must decide whether it will include both sexes in prophylactic measures, as it must also decide regarding the ages when the use of iodine should begin and end. In this climate probably the maximum of prevention, coupled with the minimum of effort, would be obtained by the administration of iodine between the ages of eleven and seventeen years. As applied to our schools this would mean beginning with the fifth grade.

**Method and Form of Administration.** As has been shown, iodine is taken up by the thyroid gland when given by mouth, by inhalation or by external application. And it makes very little difference from a scientific point of view what form of iodine is used; the thyroid gland will take up iodine from the most stable compound, *i. e.*, mercuric iodide. Weith reports favorable therapeutic results from the inhalation of iodine secured by the suspension in the school room of a wide-mouthed bottle containing 10 per cent tincture of iodine.

It has been suggested by Sloan that in these mildly goitrous districts a mixture of small amounts of sodium iodide in common table salt could be made which would suffice for all iodine therapy. However, we feel that the most satisfactory method is the individual oral administration of definite small amounts of some salt of iodine, either in solution or tablet form. For private use the well-known U. S. P. preparations, syrup of ferrous iodide and syrup of hydriodic

acid, are excellent. As described above, as a public health measure, we use 2 gm. of sodium iodide over a period of two weeks and repeated twice yearly. This dosage has prevented enlargement of the thyroid in more than 99 per cent of the children in this mildly goitrous district.

When one recalls the small amount of iodine required to saturate the normal thyroid and the specific affinity of this gland for iodine it is perfectly obvious that only very small amounts are needed. The normal thyroid contains about 5 mgm. of iodine per gram of dried gland; 25 to 30 mgm. is the total storage capacity. From this it is clear that a few milligrams of iodine daily over a longer period (a month or more) would produce optimum thyroid effects.

The prevention of thyroid enlargement in individuals with other diseases or in those residing in extremely goitrous districts as in some glacial valleys of Alaska and British Columbia, and in certain districts of the Alps and Himalayas, might require larger amounts of iodine than in normal individuals indicated above.

**Possible Ill Effects.** As was stated above there was some anxiety among medical men as to the possible ill effects of giving iodine promiscuously. Some men anticipated many cases of exophthalmic goiter while others looked for an outbreak of iodine rash. The actual results were better than we had hoped for. In all the cases taking the prescribed 2 gm. of sodium iodide twice yearly there was not a single instance of exophthalmic goiter nor any evidence of a nervous irritability simulating it. In all there were 11 cases of iodine rash, and 6 of these cases were so mild that the girls did not even stop the treatment; 5 cases, however, caused sufficient difficulty for the treatment to be stopped when the rash cleared up promptly.

Both of these possibilities were considered and mentioned in each school. In all there were over 3000 different girls taking the prophylactic treatment, many of whom took it for three years, and among these the sum total of the ill effects was a mild rash in less than 0.4 of 1 per cent.

**The Possibility of the Elimination of Endemic Goiter throughout the World.** Following the publication of the results of our first year's work in Akron the public schools of Kent and Ravenna adopted the same procedure, and in 1919 the village of Berea began the prevention of goiter through the schools on the same plan. In the spring of 1920 we completed a survey of goiter among the school children of Warren, Ohio, including all boys and girls from the fifth to the twelfth grades inclusive. As the incidence of thyroid enlargement was low—24.4 per cent in girls and 9.5 per cent in boys—we advised the school physician and nurse that we considered it sufficient in this vicinity to provide each school with a stock solution of sodium iodide and treat each goiter as soon as it was detected. This method has been in operation in Warren for one year, and is just now being started in Niles. This same method of treatment is



being practised in some of the large factories of Cleveland where many young women are employed, and it is being provided in the different factories of the National Lamp Works in eight different cities of the United States.

It is interesting to note that in the spring of 1918 Prof. R. Klinger, of Zurich, Switzerland, undertook to carry out the same treatment in the schools there. This was soon started with a different method of administration, but practically the same amounts of iodine as we used in Akron. In January, 1921, Klinger published the results of the first sixteen months' treatment, reporting extraordinary results, even though he was working in some schools in which the children were 100 per cent goitrous. Klinger's results certainly supply striking confirmation of the results we obtained in Akron. It is even more gratifying to know that recently this same plan of the prevention of goiter has been recommended to the goiter commission of Switzerland, to be carried out as a public health measure throughout the whole state, the most noted endemic goiter nation in the world.

The same imagination which developed the practical application of the principle of the prevention of goiter can now see, a few generations hence, the closing of the chapters on endemic goiter and cretinism in every civilized nation in the world.

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## THE OCCURRENCE OF PHYSICAL SIGNS SUGGESTIVE OF AORTIC DEFECTS.<sup>1</sup>

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A HEALTH survey of the police and firemen of the city of Philadelphia was recently conducted by the Henry Phipps Institute

<sup>1</sup> Read before the Thirty-eighth Annual Meeting of the American Climatological and Clinical Association, Lenox, Mass., June, 1921.

of the University of Pennsylvania, having for its objects (1) the determination of the incidence of physical defects which might reduce the efficiency of or seriously interfere with the working capacity of the individual; (2) the obtaining of information upon the value of a general health survey in the detection of disease; and (3) the securing of data in regard to the best method for conducting such an examination, the time required, cost, etc. The information was desired as the Institute was planning the establishment of a department to provide general health examinations for industrial plants in and about the city of Philadelphia.

Every member of the police and fire departments was given a complete general physical examination, including a study of the height, weight, temperature, pulse, eyes, ears, nose, throat, teeth, skin, genitalia, inguinal rings, deformities and defects, blood-pressure, heart, lungs, etc. The routine examinations were performed by Drs. John S. Scouller, H. F. Keating and William R. Gilmour under the direction of the writer of this article acting as physician-in-charge. During the examination all men who were found to be normal or whose defects were only slight were dismissed, but all those in which serious defects were detected or suspected were referred to the physician-in-charge for reëxamination, who arranged for special examinations, such as Wassermann tests, roentgen-ray examinations, electrocardiographic studies, etc., either directly or in coöperation with Dr. Hubley R. Owen, chief surgeon of the police and fire departments. The blood-pressure was taken routinely in every individual and the urine examined in every case in which the systolic pressure was 150 mm. of mercury or over, or in which the examination of the urine was indicated.

After only a small proportion of the 5706 men had passed through our hands it was found that there was a relatively large number in which the diagnostic interest was mainly centered in the aortic region. An effort was made to study these cases in detail, as far as our facilities permitted, the results forming the basis of the present paper. Special attention was given this group for the reason that it is composed of men which impressed one as being "poor risks," especially when occurring in the firemen, whose work is distinctly more strenuous than that of the policemen.

The cases under consideration were encountered under conditions which did not permit of clinical study over a long period of time, and in no case was the history of previous disease or symptomatology obtained, the cases being considered entirely on the basis of physical evidence of disease. It is, therefore, evident that we must confine ourselves to a consideration of what physical signs may be considered as definitely indicating the presumptive presence of dilatation of the aorta and what correlated evidence should be sought in an effort to discover the etiologic factor in the individual case.

**Physical Signs.** A description of the physical signs upon which a positive diagnosis of aortic disease may be based is an exceedingly difficult one, as the writers upon this subject are not in complete accord and frequently are not as clear as one would desire. This is due to the fact that their descriptions are usually confined to special diseases while the physical signs vary with the pathologic changes in the aorta.

It is not my purpose or desire to enter into a discussion of the various manifestations of arterial disease but to confine myself to a consideration of the abnormal physical signs which may be encountered in the routine examination of a large number of men, signs which suggest pathologic changes in the aorta.

The signs which have been attributed to elongation, dilatation, sclerosis or inflammation of the aorta are briefly as follows: Dulness over the manubrium, extending to the right in the 2d and 3d interspace, with or without localized pulsation recognizable by inspection or palpation.

Accentuation of the aortic second sound which may often be clanging in character or possess a tympanic quality and may frequently be accompanied by a palpable diastolic shock.

A systolic murmur may be present at the aortic cartilage which occasionally may be transmitted to the vessels of the neck and may at times be accompanied by a systolic thrill.

Others signs which have been noted are: Visible pulsation in the peripheral arteries, displacement of the right subclavian upward to a position above the clavicle, suprasternal pulsation, abnormal mobility of the apex-beat with change of position, pericardial friction rub and other signs associated with mediastinal inflammation or peri-aortitis.

The signs which have been considered of most value are manubrial dulness and alteration in tone of the second aortic sound, the latter being considered of the greatest value in recognizing aortitis in its earlier stages.

During our examination of the police and firemen we encountered 49 cases which presented evidence suggesting the presence of aortic changes. One of these, a man aged thirty-six years, with a definite specific history, showed signs definitely pointing to the presence of an aneurysm, the diagnosis being confirmed by roentgen-ray examination. This we have omitted from our series, leaving 48 cases for consideration. It will be noted that in many of the cases the records are incomplete, certain of the physical signs having apparently been omitted or not recorded. This is due to the fact that at certain periods during the examination time did not permit of as thorough an examination as one would desire or else in the rush of work the findings were not completely recorded. Failure to report for special laboratory studies, such as Wasser-

mann tests, roentgen-ray and urine examinations, largely accounts for the omissions in laboratory reports.

While these omissions may detract from the scientific value of the observations in this study, they in no way affect the primary object of this paper, which is to call attention to the relative frequency (at least in the group studied) with which physical signs may be encountered strongly suggestive of pathologic changes in the aorta. A very important feature was the almost total absence of any suspicion on the part of the individual that he was not in good health.

For convenience in presenting the cases we have arranged them in groups according to the skiagraphic findings as follows:

	Cases
Group I. Roentgen-ray shows definite aortic changes . . . . .	9
Group IIa. Roentgen-ray shows slight aortic changes . . . . .	8
Group IIb. Roentgen-ray shows questionable aortic changes . . . . .	3
Group III. Roentgen-ray shows absence of aortic changes . . . . .	13
Group IV. No roentgen-ray examination made . . . . .	15

The roentgen-ray studies were made by Dr. Alfred S. Doyle, assistant to Dr. H. K. Pancoast, roentgenologist to the University Hospital.

Tables have been prepared showing each case studied, the more important physical signs observed and such correlated clinical data as might be of interest.

The first 7 men in this group, all over forty-seven years of age, showed a definite dilatation of the aorta. A study of the physical signs recorded in these cases would indicate that the character of the second aortic sound, with a systolic aortic murmur or manubrial dulness, was the most characteristic sign of the dilatation. The 2 cases without accentuation of the aortic second were ones in which the blood-pressure was normal. (See Table I)

It must be borne in mind that the record of "accentuation of the second aortic sound" refers merely to accentuation and not to the quality of the second sound itself. These 48 cases were considered as possible cases of aortic disease on account of the fact that they presented signs which we considered indicative of aortic disease, the sign which we laid most stress upon being the clanging quality of the aortic second sound. The record of "accentuation of the aortic second sound" must not be taken to represent this change in the quality of the sound.

Of the two remaining cases one showed no dilatation but marked expansible pulsation by the fluoroscopic examination, with a systolic aortic murmur in a case of aortic regurgitation, and one showed an abnormal pulsation below the left clavicle due to a tortuous aortic arch, especially marked at this point.

GROUP I.—DILATATION OF AORTA WITH X-RAY EXAMINATION.

Case No.	Age.	Wassermann test.				Urine examination.				Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.
		Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.		
1881	52	+	+	+	+	1006	Tr.	0	..	170	90	80		
3915 <sup>1</sup>	53	+	+	+	+	1012	Pres.	0	..	205	140	65		
3207	48	+	+	+	+	1012	Tr.	+	..	140	80	60		
3039	60	+	+	+	+	1024	Ft. tr.	..	..	185	110	75		
2133	50	+	+	+	+	1024	..	..	..	205	125	80		
3725	50	0	+	+	+	1021	..	..	..	125	70	55		
3823	68	0	+	+	+	1021	..	+	130	80	50	50		
5085	41	0	+	+	+	..	..	..	155	80	75	75		
2805	41	0	+	+	+	..	..	+	120	80	40	40		

<sup>1</sup> Died suddenly since examination.  
<sup>2</sup> Has resigned (on account of ill health?) since examination.

First portion of arch broad and pulsating; mod. dilatation of entire arch, especially the ascending portion.  
 Decided widening of arch, especially pulsation.  
 Widening of aorta; no unusual pulsation.  
 Marked dilatation of arch and marked pulsation.  
 Considerable enlargement of arch and considerable descending portions of arch.  
 Increase in size of first portion of arch.  
 Dilatation of arch and marked pulsation.  
 Widening of first portion of arch and directions of first portion of arch (old tb.?).  
 Arch not dilated but marked pulsation; slight tortuosity (pulm. tuberc.?).  
 Tortuous aortic arch, especially in second left interspace.

GROUP II A.—SLIGHT DILATATION OF AORTA WITH X-RAY EXAMINATION.

Case No.	Age.	Accentuated aortic second sound.	Aortic azygotic aneurism.	Dulness over manubrium.	Wassermann test.			Urine examination.				Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.		
					Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.			Pulse pressure.	
58	41	+	+	+	+	+	+	+	+	1006	tr.	0	+	145	90	55	Prominent superficial veins over chest. Exrasytosis; aortic fibrill.	First portion of arch a little widened in both directions. Slight dilatation of ascending arch.
3922	57	+	+	+	+	+	+	+	+	1020	tr.	0	+	140	80	60	Cardiac dilatation	Slight dilatation of ascending arch. Ascending arch slightly widened in oblique position.
22	35	+	+	+	+	+	+	+	+	1020	tr.	0	+	155	95	60	Rel. mitr. insuf.; aortic fibrill. (electrocard.)	First portion of arch slightly increased in width, Aorta slightly tortuous and slightly dilated
5325	57	+	+	+	+	+	+	+	+	1020	tr.	0	+	155	90	65	Aortic and mitral regurg.	Aorta slightly tortuous and slightly dilated in ascending portion; no aneurysm.
3893	66	0	+	+	+	+	+	+	+	1010	Cl.	0	+	125	85	40	Rel. mitral insuf.	Slight increase in width of first portion of arch in both directions; pulsation not marked.
2167	51	0	+	+	+	+	+	+	+	1010	Cl.	0	+	145	80	65	Mitral regurg. ?; heart irreg.; visible pulsation in vessels.	Arch of aorta slightly increased in width.
3714	54	0	+	+	+	+	+	+	+	1010	Cl.	0	+	145	80	65	Mitral regurg. ?; heart irreg.; visible pulsation in vessels.	Arch of aorta slightly increased in width.
2068	10	0	+	+	+	+	+	+	+	1010	Cl.	0	+	145	80	65	Mitral regurg. ?; heart irreg.; visible pulsation in vessels.	Arch of aorta slightly increased in width.

GROUP II B.—QUESTIONABLE DILATATION OF AORTA WITH X-RAY EXAMINATION.

Case No.	Age.	Accentuated aortic second sound.	Aortic systolic murmur.	Dulness over manubrium.	Wassermann test.			Urine examination.				Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.
					Positive.	Negative.	Omitted.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.		
3281	53	+	+	+	+	+	+	1036	Tr.	+	+	195	95	100	Mitral insuf.	Arch possibly slightly increased in oblique view.
2590	53	+	+	+	+	+	+	+	+	+	+	125	80	45	Mitral regurg.?	Slight widening of ascending arch in ant.-post. and oblique views, but not unusual for age.
2261	11	+	+	+	+	+	+	+	+	+	+	135	80	55	.....	Good pulsation of ascending arch which is possibly slightly broadened but not to an unusual degree.

# GROUP III.—AORTIC CHANGES SUSPECTED CLINICALLY, WITH NEGATIVE X-RAY FINDINGS.

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Case No.	Age.	Wassermann test.			Dulness over manubrium.	Aortic systolic murmur.	Accentuated aortic second sound.	Urine examination.				Blood-pressure.			Associated cardiac defects, physical signs and symptoms.	Report of Roentgen-ray examination of aorta and lungs.
		Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse.	Systolic.	Diastolic.		
365	42	+	+	+	+	1005	..	..	..	155	75	80	155	75	Rel. mitral insuf.	Negative.
439	35	+	+	+	+	..	..	..	..	155	90	65	170	85	Rel. mitral insuf.	Negative.
724	53	+	+	+	+	1020	Tr.	..	..	125	75	85	160	70	Mitral regurg.	Negative.
2820	36	+	+	+	+	1015	..	0	+	130	70	90	185	85	Aortic regurg.	Negative.
4627	62	+	+	+	+	1007	V. ft. tr.	..	+	125	85	85	165	85	..	Aorta not enlarged to any unusual extent.
1889	43	+	+	+	+	1025	..	..	+	130	80	80	155	85	Soft double aortic and systolic murmur at apex; reexam. neg.	Negative.
485	29	+	+	+	+	1022	V. ft. tr.	..	+	155	95	50	155	60	Rel. mitral insuf.	Negative.
1806	37	+	+	+	+	1017	V. ft. tr.	0	..	100	55	55	100	55	Rel. mitral insuf.; chronic myocarditis	Negative.
4530	22	+	+	+	+	..	..	..	140	85	55	55	85	55	..	Negative.
5397	46	0	+	+	+	..	..	+	..	..	..	..	..	..	..	..
2272	52	0	+	+	+	..	..	+	..	..	..	..	..	..	..	..
2900	65	0	+	+	+	..	..	+	..	..	..	..	..	..	..	..
1934	52	0	+	+	+	..	..	+	..	..	..	..	..	..	..	..



GROUP IV.—AORTIC CHANGES SUSPECTED CLINICALLY, NO X-RAY EXAMINATION MADE.

Case No.	Age.	Accentuated aortic second sound	Aortic systolic murmur.	Dulness over mububrium.	Wassermann test.			Urine examination.					Blood-pressure.			Associated cardiac and pulmonary defects and physical signs.
					Positive.	Negative.	Omitted.	Normal.	Specific gravity.	Albumin.	Sugar.	Omitted.	Systolic.	Diastolic.	Pulse pressure.	
1610	63	++	+	+	+	+	++	++	1023	..	..	..	165	105	60	Myocarditis; aortic fibrill.?
1112	61	++	+	+	+	+	++	++	1010	..	..	..	185	30	155	Rel. mitral insuf.?
4526	26	++	+	+	+	+	++	++	1021	Cl.	..	..	175	85	90	Mitral regurg.?
5519	50	++	+	+	+	+	++	++	1020	V. ft. tr.	0	..	190	120	70	Mitral regurg.
471	29	++	+	+	+	+	++	++	1002	..	..	..	180	90	90	
1801	52	++	+	+	+	+	++	++	1020	V. ft. tr.	0	..	155	85	70	Cardiac hypertrophy; overact- ing heart.
1554	37	++	+	+	+	+	++	++	1007	V. ft. tr.	0	..	155	75	80	Visible pulsation in vessels.
1393	38	0	+	+	+	+	++	++	1027	Cl.	0	..	115	80	35	Mitral regurg.?
1328	11	0	+	+	+	+	++	++	..	..	..	..	105	105	60	Extrasystoles; aortic regurg.
5103	50	0	+	+	+	+	++	++	..	..	..	..	110	65	45	Mitral sten. and regurg.; mitral regurg.
841	19	0	+	+	+	+	++	++	1016	..	..	..	165	90	75	Emphysema.
2939	60	0	+	+	+	+	++	++	1020	V. ft. tr.	0	..	130	75	55	Mitral regurg.
2356	59	0	+	+	+	+	++	++	..	..	..	..	150	80	70	Mitral regurg.; aortic and mitral regurg.; aortic fibrill.?
3236	60	0	+	+	+	+	++	++	..	..	..	..	130	50	80	Marked suprasternal pulsation.
3135	44	0	+	+	+	+	++	++	..	..	..	..	..	..	..	

1 Died since examination (of uremia?).

This group consisted of 8 cases in which the roentgen-ray revealed slight increase in width of a portion of the aorta, and yet the various physical signs occurred with about the same relative frequency as in Group I. It will be noted that in this group the systolic blood-pressure was, as a rule, lower than in Group I, an average of 147 compared to 159. (See Table IIa).

Here the signs also occurred with fair constancy even in three cases with questionable roentgen-ray findings. (See Table IIb.)

This group consists of 13 men in which the roentgen-ray examination was negative, but in all of which definite physical signs were noted pointing to aortic changes. In two cases (485 and 1934) a positive Wassermann test was obtained and may be considered as cases of specific aortitis without dilatation or marked elongation of the aortic arch.

In 5 cases the Wassermann test was not made so that they may be considered as possible cases of aortitis. There were, however, 6 cases in which the Wassermann test was negative and which showed definite physical signs of aortic change with negative roentgen-ray findings. In these cases it is difficult to explain the apparent discrepancy between the physical findings and the roentgen-ray study. In 1 case there was a slight albuminuria with hypertension in a young man aged twenty-two; in 2 other cases the systolic blood-pressure was rather high for the age and in 2 the pressure was normal. (See Table III.)

There were 15 cases in which no roentgen-ray examination was made and with 3 exceptions no Wassermann test. These were nearly all cases presenting evidence of cardiac disease in addition to the suspected aortic change, many of them also showing albuminuria. (See Table IV.)

**Summary.** In the examination of large bodies of men more attention should be directed to the study of the upper anterior chest than is usually devoted to this region, especially, but by no means exclusively, in those over forty years of age. In the present study of 5706 men with an average age of forty-five to forty-nine years, signs were found suggesting changes in the aorta in about 0.85 per cent. The literature on this subject is surprisingly scanty when one considers the importance of the condition. The statement has been made by Clifford Allbutt<sup>2</sup> that "Chronic disease of the ascending aorta without aneurysm is far more common in middle life, in early adult life and even in youthful life than we are wont to realize, and is for the most part insidious." An observation which the present study would appear to confirm.

The nature of our study was of such a character that it is impossible to arrive at any very definite conclusions as regards to etiology; 5 showed a positive Wassermann reaction (including

<sup>2</sup> Diseases of the Arteries, including Angina Pectoris, 1915, 2, 190.

the case of aneurism), in 20 it was negative and in the remaining 24 it was not taken. In only 3 instances was sclerosis of the peripheral arteries (radials) noted among the 44 cases in which a positive Wassermann test was not present or not made, although the absence of sclerosis in the peripheral vessels does not exclude the possibility of aortic change. In an effort to show the type of case in which this condition was noted we have prepared the following table:

TABLE SHOWING ASSOCIATED DEFECTS (CASES WITH POSITIVE WASSERMANN TESTS BEING ELIMINATED.)

	Wassermann test negative.		Wassermann test not made.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.
Hypertension:						
Cardiorenal . . . . .	7	35.0	2	8.3	9	20.4
Cardiac . . . . .	3	15.0	4	16.6	7	15.9
Renal . . . . .	1	5.0	6	25.0	7	15.9
Alone . . . . .	1	5.0	2	8.3	3	6.8
Slight—urine not examined . . . . .	0	0	2	8.3	2	4.5
Cardiac . . . . .	0	0	5	20.8	5	11.3
Questionable . . . . .	3	15.0	1	4.1	4	9.0
None—urine not examined	5	25.0	2	8.3	7	15.9
Total . . . . .	20	100.0	24	99.7	44	99.7

It will be noted that the large proportion of cases were associated with some degree of hypertension, in 60 per cent of those with negative Wassermann test and in 64.5 per cent of those in which no Wassermann test was made. This corresponds with the observations of Smith and Kilgore,<sup>3</sup> who found frequent dilatation of the arch in their roentgen-ray study in individuals under the age of fifty years in non-syphilitic conditions, especially in chronic nephritis with hypertension.

In conclusion, we would state that in the examination of a large number of men, non-syphilitic cases are encountered with relative frequency in which the physical signs strongly suggest the presence of aortic changes, which may or may not be appreciable by roentgen-ray examination.

<sup>3</sup> AM. JOUR. MED. SC., April, 1915.

## THE HEART MUSCLE CHANGES IN PNEUMONIA, WITH REMARKS ON DIGITALIS THERAPY.\*

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THE recent article by Brooks and Carroll<sup>1</sup> upon the management of the heart in pneumonia, with reference to digitalis therapy, has stimulated an analysis of personal records of patients under the care of officers in the Medical Service of the U. S. Army Base Hospital, Fort Riley, Kansas (Camp Funston), from October 18, 1917, to December 31, 1918. Brooks and Carroll based their deductions upon an analysis of 5000 protocols of patients who died from pneumonia in the A. E. F. (Dijon). Their study consisted largely of instances of influenza pneumonia. The present series will deal with 1205 lobar and bronchopneumonia patients, including 259 autopsies. A series of 2657 patients with influenza pneumonia<sup>2</sup> treated during the interval September 15 to November 1, 1918, has been excluded from the statistics since but a relatively small number of autopsies were performed and since, because of the large number treated in a short period it was impossible to draw deductions as to the efficiency of the digitalis treatment employed.

**The Cause of Death.** Such a large proportion of pneumonia deaths have appeared to have resulted from circulatory failure that interest, from the standpoint of treatment, has largely centered upon the condition of the heart. Those of large experience in the pathology of the disease have realized that in many cases acute parenchymatous degenerative changes were commonly found to be present in many organs aside from the heart muscle. It has by no means been decided that the degenerative changes, in the degree commonly found, have been responsible for the usual death in this disease, although it may be granted that the function of the various organs, such as the liver, kidney and spleen, may have been more or less seriously disturbed. When the marked recuperative powers of the liver and kidneys are recalled in poisoning from chloroform, arsenic and other toxic agents, as well as the ability of the heart muscle to restore its normal function after prolonged serious illness, such as typhoid and diphtheria, in which degenerative changes must have occurred, the question may be raised whether in an acute pneumonia without sepsis death has resulted from the disturbed function of these organs brought about, *per se*, by the degeneration

\* Read before the American Climatological and Clinical Association, Lenox, Mass., June 4, 1921. Published by authority Surgeon-General U. S. Army.

<sup>1</sup> AM. JOUR. MED. SC., December, 1920, 160, 815.

<sup>2</sup> Swift, George W., and Stone, Willard J.: Jour. Am. Med. Assn., February, 1919, 72, 487.

found to be present. That these processes have operated to disturb function may be conceded. But that they have exerted the essential influence leading to death may be questioned in many instances. It may be believed that the matter will resolve itself into a question of extent and degree rather than kind.

Those who have witnessed any large series of pneumonia autopsies must have been impressed with the extensiveness of the septic changes such as empyema, pericarditis, substernal pus pockets, lung abscess, subdiaphragmatic abscess and peritonitis present, in one form or another, in a considerable proportion of the cases. For example, in Table I it will be noted that in 1205 cases sepsis in one form or another was present clinically, or at autopsy, in 283, or 23.5 per cent. Report has previously been made<sup>3</sup> of the occurrence of acute and subacute purulent pericarditis which was present in 58, or 19.3 per cent, of 300 pneumonia autopsies of all types, including influenza pneumonia. Of itself sepsis has appeared to be the most important cause of death in the subacute or chronic forms of the disease, that is, in those who have died after the fourteenth day of illness.

TABLE I.

	Total cases.	Sepsis.	Per cent.
Oct. 18, 1917, to Jan. 15, 1918 . . . . .	279	66	23.6
Jan. 16, 1918, to May 18, 1918 . . . . .	592	134	22.6
June 1, 1918, to Dec. 31, 1918 . . . . .	334	83	24.8
Total . . . . .	1205	283	23.5

In our experience the septic infection appeared to have spread, in most instances, by way of the lymphatics rather than by the blood stream. In a large proportion the blood cultures were sterile and we were impressed by the comparative rarity of such complications as endocarditis, septic infarction of the kidneys or the spleen and meningitis and phlebitis, which may have been regarded as evidences of blood-stream transportation.

In the consideration of those causes other than sepsis responsible for death in many acute forms of the disease, failure of the cardiac muscle to meet the demands made upon it has appeared as a prominent factor. In few other acute diseases have adverse conditions conspired to defeat the purpose of function on the part of the heart as in pneumonia. The mechanical features of obstruction to the pulmonary circuit offered by the consolidation with its consequent right heart strain, the anoxemia, toxemia and blood concentration, have all directly or indirectly operated to disturb function.

**The Heart Muscle Changes.** The protocols of 259 autopsies upon pneumonia patients in which the condition of the heart muscle was described have been analyzed. The heart-muscle changes

<sup>3</sup> Stone, Willard J.: Jour. Am. Med. Assn., July 26, 1919, 254, 73.

have been shown in Table II. It should be stated that particular interest as to the condition of the heart muscle on the part of the pathologists (Dr. Henry W. Cattell, Dr. F. K. Bartlett, Dr. S. T. Nicholson, Jr., and Dr. Arthur A. Smith, former officers in the Medical Corps, U. S. Army) was solicited because of the fact that large doses of a standardized tincture of digitalis were routinely used in the treatment of the disease.

TABLE II.

Gross changes.	Lobar pneumonia (89 autopsies), per cent.	Broncho- pneumonia <sup>4</sup> (112 autopsies), per cent.	Sepsis following pneumonia (58 autopsies), per cent.
Heart muscle normal . . . . .	57.3	66.1	37.9
Heart muscle degeneration . . . . .	42.4	33.9	62.1
Right ventricle dilatation . . . . .	39.4	36.6	20.8
Left ventricle dilatation . . . . .	12.4	10.0	12.1

It will be noted that in 89 lobar pneumonia autopsies dilatation of the right ventricle was found in 39.4 per cent, while in 112 bronchopneumonia autopsies, which included interstitial and confluent lobular types, dilatation of the right ventricle was found to be present in 36.6 per cent. The left ventricle was found to be dilated in 12.4 per cent of the lobar pneumonia and in 10 per cent of the bronchopneumonia autopsies. In 58 autopsies upon patients who died as a result of sepsis following pneumonia the right ventricle was found to be dilated in 20.8 per cent. A majority of these patients had recovered from their acute pneumonia.

These figures are higher than those reported by Berry<sup>5</sup> in his analysis of 400 pneumonia autopsies performed at the Boston City Hospital. He found that cardiac dilatation was reported by the pathologists but 6 times in the 400 cases. It would be interesting to know what criteria served to establish the diagnosis of dilatation, or the absence of it, on the part of the various pathologists who performed the autopsies over the period of years mentioned in the report, for it is difficult to believe that dilatation only occurred in less than 1 per cent of the cases.

In the present series the gross appearance of the heart muscle was described as normal in 57.3 per cent of the 89 lobar pneumonia autopsies while degenerative changes were believed to be present in 42.7 per cent. In the 112 autopsies upon bronchopneumonia patients (including the interstitial and confluent lobular types) the gross appearance of the heart muscle was described as normal in 66.1 per cent, while degenerative changes were noted in 33.9 per cent. Brooks and Carroll in the Dijon study have reported that an inflammation or degeneration of the heart muscle was present

<sup>4</sup> Under the term bronchopneumonia have been included confluent lobular and interstitial types.

<sup>5</sup> Medical Clinics of North America, September, 1920, 4, 571.

in 748 of 1651 protocols, or 45.3 per cent. As would be expected in the 58 autopsies upon patients who died with sepsis following pneumonia (such as empyema, purulent pericarditis, multiple lung abscesses, substernal pus pockets, subdiaphragmatic abscess, peritonitis or meningitis) evidences of heart-muscle degeneration were present in a larger number, 62.1 per cent.

**The Microscopical Findings.** The sections of heart muscle from 34 autopsies upon lobar pneumonia patients and from 37 autopsies upon bronchopneumonia patients (including the confluent lobular and interstitial types) have been studied. The specimens were prepared under the direction of Dr. O. F. Broman, formerly chief of the laboratory service in the hospital. The findings have been presented in Table III.

TABLE III.—MICROSCOPICAL FINDINGS.

	Lobar pneumonia (34 autopsies), per cent.	Broncho- pneumonia <sup>*</sup> (37 autopsies), per cent.
Heart muscle normal . . . . .	20.6	40.5
Parenchymatous degeneration . . . . .	52.9	37.8
Fatty degeneration . . . . .	11.7	8.1
Leukocytic and round-cell infiltration . . . . .	8.9	10.8
Hyaline degeneration . . . . .	2.9	
Interstitial myocarditis . . . . .	2.9	2.7

Parenchymatous degeneration (cloudy swelling) was present in 52.9 per cent of the sections in lobar pneumonia and in 37.8 per cent of the sections in bronchopneumonia. As will be noted in the table other degenerative changes were more marked in the lobar pneumonia than in the bronchopneumonia sections. Fragmentation of the muscle fibers was not described as a condition necessarily of pathological importance, even though extensive in some of the sections, because of its occurrence in many apparently normal specimens.

**Digitalis Therapy in Pneumonia.** Beginning January 15, 1918, all patients with pneumonia received during the first twenty-four to thirty-six hours after admission to the hospital their total dosage, according to estimated body weight, of a special tincture of digitalis prepared in the hospital by Sergeant Moody, in charge of the pharmacy. The tincture was standardized by the cat method of Hatcher<sup>7</sup> through the kindness of Dr. Cary Eggleston, of Cornell Medical School. The tincture was prepared from Allen's English leaves as follows: The entire contents of the one-pound cans were finely ground and percolated with 75 per cent alcohol. Since the cans were hermetically sealed and moisture and molds have been known to cause deterioration in the leaves after the cans were opened

<sup>\*</sup> Including confluent lobular and interstitial types.

<sup>7</sup> Am. Jour. Pharm., 1910, 82, 360.

the tincture was made up in large quantity, using the entire contents of the cans and avoiding cans opened for previous batches which may have contained small quantities of left-over leaves. Many batches of tincture so prepared preserved their potency for a year when kept under conditions of ordinary care. The tinctures standardized uniformly well. So far as can be recalled all batches closely approximated in dosage 0.15 of one cat unit (0.15 cc) per pound of the patient's body weight with three exceptions, two of which were weaker, standardizing to a dosage of 0.17 cc and the other to 0.10 cc per pound of the patient's body weight. Emphasis has been placed upon the point of careful percolation in the preparation of the tincture together with the caution to use the entire contents of the sealed cans, since it has been believed to be the common practice of pharmacists to make up their tinctures of digitalis in small batches. Since a one-pound can of leaves will make ten pounds of tincture the can of leaves may not be sealed after opening and may be reopened four or five times in the course of as many weeks or months, each time with the admission of moisture and molds. Failure to observe these points has been responsible, it is believed, for many low standard tinctures as obtained in the market.

Because of closer medical observation in military organizations, patients with pneumonia were admitted to the hospital with much less delay than would have occurred under similar conditions in civil life. There were comparatively few instances of delay in admission during the initial stage of the disease, and these were due to the desire on the part of the soldiers to minimize or conceal sickness in order to keep up with the training. The dosage was administered as follows:

If the tincture in use standardized to 0.15 cc per pound of weight and the patient weighed about 160 pounds he received a total dosage of 24 cc. This was usually given in 4 cc doses every four hours for six doses. Administration was then stopped. This plan was not followed if the patient had received digitalis medication in any form during a period of ten days preceding. As a rule there was no marked slowing of pulse-rate after such doses had been given. This was in accord with the observation of Cohn<sup>8</sup> that slowing of the pulse-rate was not a primary effect of digitalis in therapeutic doses in hearts with normal sinus rhythm. There were but few instances of nausea, which occurred as a toxic effect when enough had been given in susceptible individuals to physiologically affect the medullary center. Partial heart-block of transitory duration occurred but once and coupled beats or frequent premature contractions as evidence of toxic effect were not common. If present these symptoms usually promptly subsided when atropin in 1-100 to 1-75 grain doses were given. A transient rise of blood-pressure

<sup>8</sup> Jour. Am. Med. Assn., October 30, 1915, 65, 1527.



sometimes occurred. In one instance the systolic blood-pressure reached 190 mm. There was, as a rule, less change in the diastolic pressure. Diuresis was the most constant evidence of absorption and effect. Since fluids were forced as part of the treatment during the fever to prevent dehydration and blood concentration, the diuretic effect of digitalis in the absence of edema was, however, difficult to determine in many patients.

If further dosage were believed necessary, after four or five days, because of the clinical evidence of a dilated heart, the earlier amounts were supplemented by intravenous injection of digipuratum when obtainable, by digitalone or by the oral use of Nativelles's crystalized digitaline. On the latter preparation the dose required for full effect was 1 granule per 10 pounds of the patient's weight, providing no other form of digitalis had been given during the preceding ten days. If used to supplement the dosage of the tincture, as outlined above, not over one-half the estimated number of granules were given. Those interested in the use of standardized preparations for digitalis administration should consult the articles of Eggleston.<sup>9</sup>

TABLE IV.—PNEUMONIA MORTALITY.

Period.	Cases.	Deaths.	Per cent.	Remarks.
Oct. 18, 1917, to Jan. 15, 1918 . . . . .	...	...	....	Incidence of sepsis = 23.6 per cent.
With sepsis . . . . .	66	61	92.4	Digitalis not routinely used.
Without sepsis . . . . .	213	55	25.8	
	279	116	41.5	
Jan. 16, 1918, to May 18, 1918 . . . . .				
With sepsis . . . . .	134	69	51.5	Incidence of sepsis = 22.6 per cent.
Without sepsis . . . . .	458	54	11.8	Digitalis used.
	592	123	20.7	
June 1, 1918, to Dec. 31, 1918 . . . . .				
With sepsis . . . . .	83	31	37.3	Incidence of sepsis = 24.8 per cent.
Without sepsis . . . . .	251	22	8.7	Digitalis used.
	334	53	15.8	

**The Results of Digitalis Therapy.** Digitalis therapy in pneumonia was carried out in this manner because it was believed that circulatory failure had occurred in about one-fourth of the deaths, in which sepsis had not appeared to be a factor, for the period immediately preceding October 18, 1917, to January 15, 1918.<sup>10</sup>

<sup>9</sup> Arch. Int. Med., July, 1915, 1, 16. Jour. Am. Med. Assn., March 13, 1920, 74, 733.

<sup>10</sup> Phillips, Bruce G., Bliss, Walter P., and Stone, Willard J.: Arch. Int. Med., October, 1918, 22, 409.

It will be noted in Table IV that during this period when digitalis was not routinely used, 55 deaths, without evidence of sepsis, occurred among 213 pneumonia patients; that is, 25.8 per cent of the deaths were believed to have been associated with cardiac failure. This belief was found upon a clinical review of many of the histories and upon the autopsy findings. Cohn<sup>11</sup> had previously expressed the opinion that digitalis acted the same in pneumonia as in non-febrile conditions. It should be mentioned that Type I antiserum was used intravenously in all pneumonia infections due to Type I pneumococcus, and that through the kindness of Dr. Preston Kyes, of the University of Chicago, we were supplied with his antipneumococcus chicken serum, which was used in the treatment of many patients with pneumococcus infections of other types.

With due regard for the pitfalls of statistical comparisons an attempt has been made to analyze the figures shown in the preceding table. It will be observed that during the period when digitalis was first used (January 16 to May 18) there was a decrease in the number of deaths believed to have been associated with cardiac failure to 11.8 per cent and for the second period (June 1 to December 31) to 8.7 per cent. The point may be raised that each of these intervals may have covered different phases of virulence of or susceptibility to the organisms responsible for the disease. Other unknown factors may have influenced the results, but it may be mentioned that a remarkable constancy of infective types was present from month to month during these periods. For example, it was shown<sup>12</sup> that among a series of 310 empyema operations (subsequent to pneumonia) during these periods streptococcus (largely hemolyticus) and pneumococcus infections were responsible for the condition as follows:

TABLE V.—INFECTIVE ORGANISMS ISOLATED IN EMPYEMA.

Period.	Number of cases.	Streptococcus, per cent.	Pneumococcus, per cent.
Oct. 20, 1917, to Jan. 21, 1918 . . . .	71	73.2	26.7
Jan. 12, 1918, to Aug. 10, 1918 . . . .	95	73.6	26.3
Oct. 18, 1918, to Feb. 14, 1919 . . . .	85	70.4	29.4

It will also be observed in Table IV that the incidence of sepsis, as the largest single factor responsible for death also showed remarkable constancy during the one period when digitalis was not routinely used and for the two subsequent periods when the drug was used. In the first the incidence of sepsis was 23.6 per cent, in the second 22.6 per cent and in the third 24.8 per cent. It may therefore be believed that there was no marked variation in the virulence of the infection causing the disease during those compared periods.

<sup>11</sup> Loc. cit.

<sup>12</sup> Stone, Willard J.: AM. JOUR. MED. SC., July, 1919, 158, 1.

The reduction in mortality of patients with sepsis during the last two periods (Table IV) was believed to have resulted from improvement, with increasing experience, in the method of treatment. This refers particularly to empyema. In the first period early operation was performed as soon as pus was found in the pleural cavity. This resulted in a high mortality because of collapse of the lung incident to an open pneumothorax which was many times associated with an active pneumonic process in the opposite lung. During the last two periods early aspiration was repeatedly performed followed by late operation after the activity of the pneumonic process had subsided and after, it was believed, relative immobilization of the mediastinum had occurred. Such procedure diminished the danger of an open pneumothorax when made of sufficient size to secure adequate drainage.

In connection with digitalis therapy in pneumonia it was believed rational, if used at all, to secure effect early before the heart had become incompetent through dilatation or muscle degenerative changes with consequent exhaustion of its reserve tonicity. The tincture was found by Haskell, McCants and Gardner<sup>13</sup> to have been better absorbed from the gastro-intestinal tract than the infusion. Cohn<sup>14</sup> has shown that in dogs and cats with doses of therapeutic range equal to 30 per cent of the calculated lethal dose, digitalis increased the contractile function of the cardiac muscle, and by so doing increased the volume output. In pneumonia any treatment which would beneficially affect the volume output of the heart would be highly desirable, since Hoover<sup>15</sup> has shown that oxygen unsaturation existed to greater or less degree in every pneumonic consolidation, a condition augmented by shallow breathing, diaphragm immobility and asynchronism, all of which would tend to interfere with an adequate blood supply to the cardiac and respiratory centers in the medulla.

Pardee<sup>16</sup> has shown that the body disposed of digitalis at an average rate of about 1.3 cc of the tincture per day. In many digitalized pneumonia patients of this series when it was believed four or five days later, upon clinical evidence, that more of the drug was indicated, 20 to 25 per cent of the earlier estimated dosage was additionally given with the point in mind that elimination had disposed of such an estimated proportion of the total amount. If digitalis should be used in pneumonia it would seem futile to give it routinely in doses of five minims of the tincture by mouth three or four times daily, as has been advocated by various authors. A carefully made tincture from potent leaves may be estimated, without standardization, as having an average activity of 100 mg. to the cat unit. Since

<sup>13</sup> Arch. Int. Med., 1916, 18, 235.

<sup>14</sup> Tr. Am. Soc. Clin. Investig., Jour. Am. Med. Assn., 1920, 74, 1597.

<sup>15</sup> Jour. Am. Med. Assn., September 14, 1918, 71, 830.

<sup>16</sup> New York Med. Jour., December 27, 1919, No. 26, 110.

the total amount required for effect may be taken to equal 0.15 of one cat unit (0.15 cc) per pound of body weight a total dosage of 24 cc would be required for an adult of 160 pounds. If it is assumed that five minims equal 0.3 cc it will be readily seen that 80 doses would be required. Eighty doses of five minims four times daily would require twenty days for completion, a condition approximating absurdity if definite prompt digitalis effect were desired. On the other hand, after digitalization by full dosage has been secured, perpetuation of the effect, after a week or ten days, may be secured by the administration of smaller doses equaling the amount Pardee<sup>17</sup> has shown the body eliminates daily, that is, 1.3 cc (approximately 20 minims). It has been difficult to understand how clinicians have been able to assure themselves of definite digitalis effect from such small doses as those mentioned above, except when used to supplement full dosage given earlier. Eggleston<sup>18</sup> has mentioned certain safeguards in administration by this method to which I wish to subscribe. They were briefly as follows: Caution should be used in administering large doses if the patient had received digitalis in any form during the preceding ten days; nausea or vomiting, except when due to splanchnic congestion, present before treatment was begun, should stop the dosage, as should also a decrease in the heart-rate to 60 or below per minute. The drug should be stopped if frequent premature contractions, definite heart-block or coupled beats occur.

The writer has been under obligation to Dr. Ezra Bridge for painstaking assistance and verification of the autopsy records used in the compilation of the statistics.

**Summary.** 1. An analysis of the data secured by the study of 1205 patients with lobar and bronchopneumonia has been attempted with reference to the digitalis therapy.

2. Two hundred and seventy-nine patients with pneumonia did not receive routine digitalis therapy while 926 patients received full dosage of a potent tincture standardized by the cat method of Hatcher.

3. The gross heart-muscle changes as shown in 259 pneumonia autopsies have been described together with the microscopical study of 71 heart-muscle sections.

4. The influence of these changes upon the probable cause of death has been discussed together with the benefit believed to have been secured in treatment by the use of digitalis.

**Conclusions.** Sepsis in pneumonia was the most serious complication and the most frequent cause of death in the subacute or chronic forms of the disease; that is, among those who died as late as the fourteenth day of illness or subsequently. Among 283 patients in whom sepsis occurred there were 161 deaths, a mortality rate of

<sup>17</sup> Loc. cit.

<sup>18</sup> Loc. cit.

56.8 per cent, while among 922 pneumonia patients without sepsis there were 131 deaths, a mortality rate of 14.2 per cent.

2. Among the causes other than sepsis responsible for death in many acute forms of the disease, cardiac-muscle failure appeared to have been a prominent factor.

3. Right ventricle dilatation was found to have occurred in 39.4 per cent of 89 lobar pneumonia autopsies and in 36.6 per cent of 112 bronchopneumonia autopsies.

4. Parenchymatous, fatty and hyaline degeneration or evidences of inflammatory reaction in the heart muscle were found in 79.3 per cent of the sections from 34 lobar pneumonia autopsies and in 59.4 per cent of the sections from 37 bronchopneumonia autopsies. The extent of these changes when considered with the right ventricle dilatation was believed in many instances to have been responsible for the circulatory failure which had occurred. In other instances the extent of the degenerative changes was less marked; in the absence of dilatation of the ventricles it appeared doubtful whether these changes, in the degree found, could have so disturbed function as to produce death.

5. The mechanical obstruction to the pulmonary circulation in extensive or massive consolidation was apparently a factor of great importance in producing right ventricle dilatation.

6. Among 213 patients without sepsis in pneumonia who were not treated by the early routine administration of a standardized tincture of digitalis the percentage of deaths believed to have been associated with cardiac failure was 25.8.

7. Among 709 patients without sepsis in pneumonia who were treated by the early routine administration of a standardized tincture of digitalis the percentage of deaths believed to have been associated with cardiac failure was 10.7.

8. The susceptibility of certain individuals to digitalis action in small dosage should be borne in mind, particularly those who manifest myocardial sclerotic changes. It should be given in large doses to elderly pneumonia patients with caution.

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#### IMMEDIATE RECOVERY FROM EARLY DIABETES INSIPIDUS AFTER LUMBAR PUNCTURE. REPORT OF A CASE.

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VERY-few instances of complete recovery from diabetes insipidus after lumbar puncture have been recorded in medical literature. We are accustomed to regard the polyuria and polydipsia which so frequently accompany disturbances of the pituitary gland as

symptoms of gradual, insidious onset associated with skeletal, metabolic and sexual changes. A dysfunction of this gland structure resulting in such fundamental anatomical and physiological perversions would of necessity be of long standing, and there is no doubt that most lesions of the pituitary gland are traumatic or neoplastic in origin; are more or less destructive in nature; and are accompanied by years of functional disturbance. On the other hand, suppression or alteration of pituitary function might result from the presence of an acute inflammatory process with plastic exudate or from a transient edema of the pituitary gland. Such a transient condition might account for the gradual or rapid cure of diabetes insipidus which occasionally follows the lowering of intracranial pressure by spinal puncture. Such pathological conditions of the pituitary gland may include all grades of glandular disturbance from an acute hemorrhagic infection with rapid death to a simple and transient edema. The former condition can be diagnosed correctly only at autopsy and the latter by its transient character and the early results of therapy.

The majority of investigators agree that a secretion from the pars intermedius and pars posterior of the pituitary gland in some manner or other exerts a restricting influence upon the volume output of urine. Should we accept the theory of Dr. Harvey Cushing and his associates that the pituitary secretion reaches the third cerebral ventricle by way of the infundibulum cerebri, then we can conceive that an obstruction to the flow would be produced by a local edema or by a plastic exudate and that a like obstruction would result from increased intracranial pressure due to any cause. In other words, an increased turgescence of the infundibular stalk or the back pressure from either a mild or severe hydrocephalus could act as a partial or complete obturator to the secretory flow from the pituitary gland. Even if one accepts this hypothesis, however, why a transient disturbance of pituitary function with diabetes insipidus does not commonly occur or is not more frequently recognized, remains a mystery.

Before reporting the author's case it is of interest to offer a *resume* of three cases reported in the literature, in each of which striking results followed a lowering of the intraspinal and hence of the intracranial pressure.

1. In a case reported on June 22, 1916, by Dr. Evarts Graham,<sup>1</sup> diabetes insipidus had existed for about two months before the patient was examined. The patient, a male, aged twenty-four years, could assign no cause for the disturbance except a blow on the chest suffered about a month and a half before the onset of polyuria. On lumbar puncture the fluid was found to be under markedly increased pressure—shooting out in a steady stream for

<sup>1</sup> Jour. Am. Med. Assn., 1917, 69, 1499.

a distance of from eight to twelve inches. Following this procedure the patient was bedridden for four days with a severe headache. At the expiration of this period he went home but returned to the hospital for five days, during which period the headache gradually disappeared. The polyuria ceased shortly after the intracranial pressure was relieved. The patient's progress after leaving the hospital was not noted.

2. A case of diabetes insipidus of four years' duration was reported by Dr. J. B. Herrick<sup>2</sup> in July, 1912. The patient, a male, aged forty-three years, complained of marked thirst and frequent urination. During spinal puncture the fluid escaped very slowly under low pressure, and less than 5 cc were withdrawn. This procedure was followed by great prostration, with severe headache and pain in the back of the neck, associated with anorexia, vomiting and general malaise. The pain was so intense that morphine was given. When the prostration disappeared and fluid and food were again freely taken the thirst and the output of of urine were found to be normal. Likewise, frequent attacks of petit mal which existed prior to lumbar puncture disappeared; however, Dr. Herrick was informed by the family physician three months later that these symptoms were returning.

3. A case of diabetes insipidus of about one year's duration, which had been relieved by spinal puncture, was reported recently by Dr. P. J. Cammidge.<sup>3</sup> The patient, a male, aged forty-two years, had been troubled with marked thirst and polyuria for fully a year before examination. About one ounce of spinal fluid, under great pressure, was removed with a needle. This event was followed by a severe headache which persisted for four days. The frequent urination rapidly disappeared, so that in a week or two the nocturnal urination had ceased. There was no recurrence of symptoms after six years.

The author's case, a male, aged twenty-seven years, was referred by Dr. R. G. Pearce, of the department of health of the B. F. Goodrich Company, Akron, Ohio. The patient came in for examination on November 26, 1920, complaining of the frequent voiding of large quantities of urine associated with great thirst. Abdominal discomfort resulting from a full bladder, had awakened him at 4 o'clock on that morning. This was immediately relieved after urination, but he was obliged to empty his bladder twice more before 6 A.M., and each time he passed a large amount of urine. Thereafter he voided copiously about every twenty minutes, even retiring frequently for relief during the physical examination.

Another symptom which persisted from the time of onset was a heavy "dry" feeling behind the bridge of the nose. As he stated it, "I feel as if trouble here is causing my thirst." He also noted

<sup>2</sup> Arch. Int. Med., 1912, 10, 1-7.

<sup>3</sup> Practitioner, 1920, 105, 244-247.

marked sweating of the body, hands and feet, so that a wet undershirt and soaked stockings and shoes made him feel as if he had fallen into a pool of water. Aside from these complaints the patient felt as well and active as ever, with no headache, disturbance of vision or real pain anywhere.

*Past History.* The patient had had typhoid fever at the age of ten years. In January, 1918, he was under observation for pulmonary tuberculosis, but was eventually discharged as negative. However, for the sake of safety, he went West for a couple of years and lived outdoors. He acquired influenza in February, 1920, but made a good recovery. Since then his health had been excellent. There was no history of venereal infection. He had been married four years. His wife and one child were living and well.

*Family History.* The patient's father and mother were living and well. He had four brothers and sisters, all living and in normal health. There had been no history of tuberculosis, insanity or diabetes in the family. All his grandparents lived to be over seventy-five years of age, except the paternal grandmother, who died at the age of fifty-seven years, cause of death unknown.

*Physical Examination.* The author's examination of the patient made four hours after the onset of the polyuria may be summarized as follows: Temperature, 97°; pulse, 70; respirations, 20; patient of medium size and build, well-developed and well-nourished, with no apparent loss in weight; mental condition alert with no undue nervousness; marked sweating of hands, body, legs, and feet, but none on the face or the neck; the shirt, stockings and shoes were soaking wet.

*Head.* No tenderness over the sinuses; slight ptosis of the left upper eyelid; visual fields normal to the finger test, but perimetry revealed slight concentric narrowing in the left eye; no external ophthalmoplegia; pupils equal, regular, centrally placed and reacting well to light and accommodation; vision normal by Snellen's test card; septum of nose markedly deviated to the left with absence of sense of smell on that side; slight hyperesthesia to cotton wool over the distribution of the left fifth cranial nerve; facial muscles and those of mastication negative; hearing in the left ear definitely diminished to a watch tick, with a lessened bone conduction; eardrums normal; tongue protruding in the midline; speech normal; power in sternocleidomastoids and trapezii muscles equal on both sides; teeth and tonsils negative; no evidence of increased salivation or lachrimation.

*Thyroid gland* palpable but not enlarged. All lymph glands of normal size.

*Thorax* symmetrical, expansion of upper and lower ribs as well as flaring of subcostal margins symmetrical.

*Lungs* negative.



*Heart* of normal size; no adventitious sounds; rate, 70.

*Pulse* rhythmic, regular, symmetrical, synchronous, with normal anacrotus and katarctus.

*Blood-pressure.* Systolic, 134; diastolic, 84. Abdomen and genitalia negative.

*Reflexes.* Biceps, triceps, patellar and tendo Achillis equal and active; corneal, epigastric, abdominal, cremasteric and plantar reflexes all symmetrical and normal; no sensory disturbance in the skin except as noted above in the distribution of the left fifth cranial nerve; no Romberg, Babinski, Chaddock or Oppenheim; no acro- or approximo-ataxia in the upper or the lower extremities; no dysdiadokokinesia.

*Urine.* 2000 cc passed between 11 A.M., and 1 P.M., on the first day; clear; faint; yellowish tinge; acid; specific gravity, 1000; albumin, none; sugar, none; microscopical examination, negative.

*Roentgen-ray Examination.* Sella turcica normal in size and contour; skull negative for visible tumor; facial sinuses all of normal density; teeth, no caries or apical abscesses.

*Eye-grounds.* Left nerve-head more pale than normal, otherwise normal.

*Blood Count.* Red corpuscles, 5,800,000; white corpuscles, 7200; hemoglobin, 100 per cent (Tallquist).

On the second day the patient was referred to Lakeside Hospital and placed under the care of Dr. C. D. Christie. From 4 P.M., of that day to 7 A.M., of the following day the urinary output was 4100 cc, with a fluid intake of 5970 cc.

A lumbar puncture for diagnostic purposes was performed two days later, on November 30, 1920, four days after the onset of the symptoms. Eight cc of clear spinal fluid were removed under normal pressure. Examination of the spinal fluid showed a cell count of 2 mononuclears per cubic millimeter; globulin, negative (Noguchi, Pandy and Ross-Jones); Wassermann test on blood and spinal fluid, negative. Phenolsulphonephthalein output of kidney (after spinal puncture) amounted for the first hour to 100 cc (40 per cent), for the second hour to 500 cc (17 per cent), making the total for two hours 600 cc (57 per cent).

Two days later the Mosenthal nephritic test was made, showing the specific gravity of the day urine to be 1020 to 1026; of the night urine, 1032; with a total urinary output during the day of 306 cc, and during the night of 100 cc, and a liquid intake for the twenty-four hours of 1200 cc.

Thus on the second day after lumbar puncture the total urinary output for twenty-four hours was 406 cc as compared with 4100 cc during fifteen hours before the lumbar puncture; while the fluid intake during the latter period was 1200 cc as compared with 5970 cc during the first cited period. The specific gravity of the urine showed a corresponding alteration from 1005 and

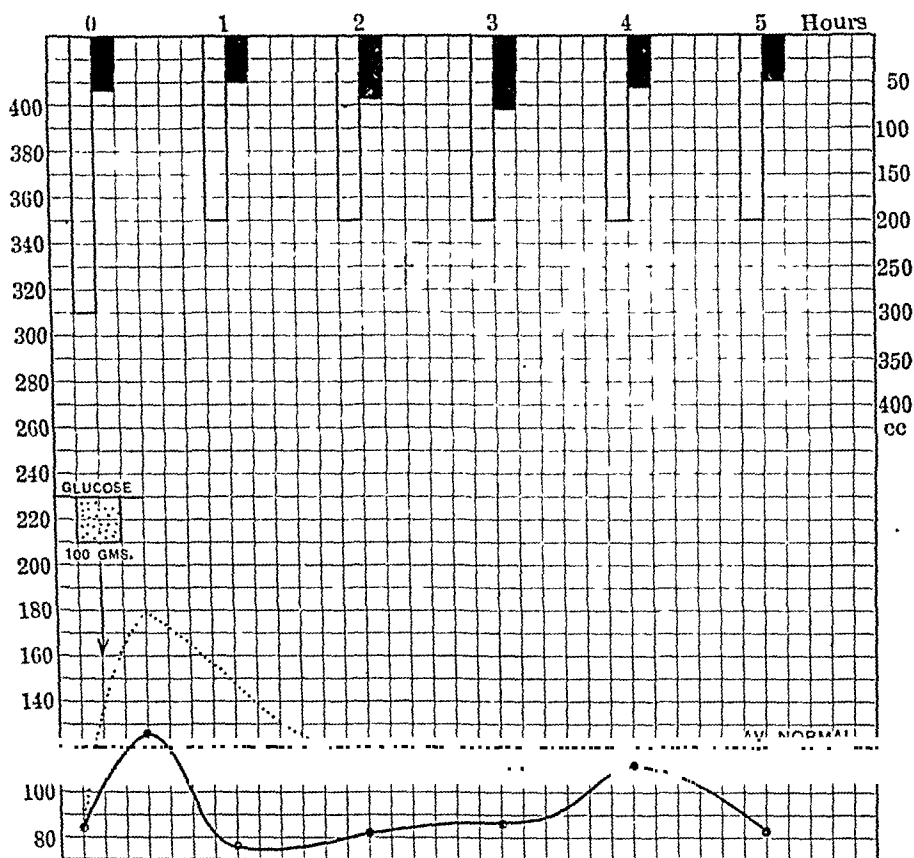
1006 before the spinal puncture to 1030 immediately after, remaining at from 1026 to 1030.

The temperature was increased to 100° and 101° F. on the second and third days after the lumbar puncture, returning to normal on the fourth day.

For five days after the removal of the subarachnoid fluid the patient had a severe headache, and he was troubled with insomnia and did not feel physically fit for a period of twenty days. Dur-

Sugar mg.  
100 cc.

Urine.



Blood-sugar curve typical of hypopituitarism shown by author's case. (Compare with normal curve shown by dotted line.) The black oblong spaces at the top indicate urinary output; the uncolored oblongs indicate water intake.

ing this time the neurological signs gradually subsided and neither then nor since was there any recurrence of the polydipsia or polyuria. About two weeks later he developed herpes on both the upper and lower lips following an acute rhinitis. This was followed in a few days by pain under the right eye. Roentgenographs of the sinuses showed a dense clouding of the left antrum. This was tapped and a large amount of pus evacuated. Within a week

after irrigation of this sinus was begun the patient felt as well as ever and all of his neuralgic pain disappeared.

A careful examination of the patient on May 3, 1921, five and a half months after the onset of diabetes insipidus, gave normal findings throughout. He has been well and very active for over four months and has had no recurrence of his thirst or frequent urination since the spinal puncture made four days after the onset of the polyuria. The chart shows the curve of sugar tolerance at the date of this last examination. There was no hyperglycemia at any time after the ingestion of 100 gm of glucose, and at its peak the blood sugar rose only to the maximum normal level. This curve is typical of that shown by cases of hypopituitarism. However, there is no other present indication of a deficiency of pituitary secretion.

The following appear to be the significant features in the history of this patient:

1. A sudden onset of diabetes insipidus without any immediate preceding illness.

2. The subjective symptoms were a sense of discomfort behind the glabella, increased thirst, a disquieting volume in urine output and marked sweating of the body and extremities.

3. Physical examination confirmed the subjective symptoms, and, in addition, revealed involvement of the first (?), second, fifth and eighth cranial nerves on the left side.

4. Within twenty-four hours after lumbar puncture the great thirst was relieved, the urinary output was reduced to normal and the sweating ceased.

5. Examination five and a half months after the onset of the diabetes insipidus gave negative findings with the exception of laboratory evidence for hypopituitarism, revealed by the very high sugar tolerance.

What was the probable cause of the diabetes insipidus in this case? (a) That it was not an acute infectious process is shown by the absence of fever, leukocytosis or any other symptom prior to the spinal puncture; (b) that it was not a brain or pituitary tumor is shown by the absence of increased pressure of the spinal fluid and the absence of choked disk in either eye, together with the magical subsidence of symptoms after the puncture and the non-recurrence in five and a half months; (c) the hyperidrosis undoubtedly resulted from a transient stimulation of the bulbar-autonomic or higher centers of sweat control.

In view of these facts it seems probable that in this case the disturbance was due to a serous meningitis with edema of the infundibulum cerebri and involvement of certain cranial nerves on the left side. The removal of 8 cc of subarachnoid fluid, even though this was under normal pressure, was adequate to restore

proper circulatory equilibrium. While this conclusion is of necessity entirely speculative, nevertheless the fact remains that whatever the pathological process may have been, it was sufficiently mild in character for complete relief to be secured.

**Conclusions.** 1. Diabetes insipidus may result not only from destructive lesions of the pituitary gland but from any cause which may obstruct the flow of the normal secretion.

2. Such an obstruction may result from a transient edema of the pituitary gland or from an inflammation with resultant plastic exudate, or it may result from extrapituitary conditions, such as increased intracranial pressure from any cause.

3. The withdrawal of spinal fluid, whether under high or low tension, tends to relieve this pressure and to remove the obstruction.

4. The experience of the author, in whose case there has been no recurrence of symptoms five and a half months after no other treatment than lumbar puncture, indicates that in any case of diabetes insipidus the patient should be given the advantage of the possibility of early relief by this means.

## THE CLINICAL, BACTERIOLOGIC AND PATHOLOGIC FINDINGS IN A CASE OF INFLUENZAL MENINGITIS.

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APPARENTLY the first authentic case of influenzal meningitis was reported by Slawyk,<sup>1</sup> in 1899, working under the direct supervision of Pfeiffer. Occasional cases occurring thereafter are described in the literature. Writing in 1910, Simon<sup>2</sup> collected 12 instances of this disease.

Martha Wollstein,<sup>3</sup> in 1911, produced in monkeys lesions simulating influenzal meningitis. She made a review of the literature, tabulating 49 cases of pure influenzal infections. Torrey,<sup>4</sup> Dunn<sup>5</sup> and Koplik<sup>7</sup> added 30, 4 and 6 cases respectively. Stone<sup>8</sup> summarized 13 others and reported a case of his own in 1920. Early in 1921, Neal<sup>9</sup> again reviewed the literature and discussed 32 cases, previously unreported. Since the time of her paper there have been recorded but 2 authentic instances of uncomplicated influenzal infection of the meninges, these being described by Litchfield<sup>10</sup> and Caprario.<sup>11</sup>

There have been, as far as we have been able to determine, 150

cases reported. We wish to submit, in addition, the following record:

This case came under observation on the medical service of the Infants' Hospital on June 12, 1921.

*Family History.* Essentially negative throughout. The patient was the last of six normal pregnancies. There was no history of exposure to tuberculosis or recent contagious disease or "colds" in the family.

*Past History.* Full term at birth and delivery was normal.

*Feeding.* Entirely breast-fed for six months, after which the infant was started on the ordinary infants' diet in addition to breast-feedings, which have been continued until the present. Has gained normally in weight throughout, without evidence of digestive difficulty until the beginning of the present illness.

*Development.* Sat up alone at five months; walked at ten months and said a few short words at fifteen months. Dentition normal.

*Illnesses.* No previous illness.

*Present Illness.* Nine days before admission the baby had a "bad cold," with a nasal discharge, sneezing and slight cough, which continued with diminishing severity for five days. He had apparently completely recovered, when two nights ago he awoke with a "high fever" and vomited small amounts of breast milk on two occasions. Was restless and cried a great deal, and had a pronounced thirst. There has been no further vomiting, but the child has taken feedings very poorly and the bowels have been markedly constipated. He turned constantly from side to side and grunted with pain when handled. There has been no noticeable retraction of the head. He was seen by the local physician, who diagnosed the case as "epidemic meningitis," and was referred to the hospital.

*Physical Examination.* Well-developed and nourished male infant of seventeen months, without noticeable loss of subcutaneous fat. He dozed frequently during the examination but awakened with a cry of pain when any attempt was made to flex the neck or manipulate the lower extremities. There was cervical adenitis, but no deformity of the bones or the joints.

*Head.* Showed both fontanelles completely closed with no external evidence of hydrocephalus.

*Facies.* Apathetic; cheeks flushed.

*Eyes.* Pupils reacted normally to light, equal and regular. There was no conjunctival discharge.

*Ears.* Showed no discharge, but on otoscopic examination a pair of markedly injected drums were disclosed, with pronounced bulging in the posterior-superior quadrant.

*Nose.* Showed purulent discharge.

*Mouth.* Teeth were normal; mucous membranes flecked with *sordes*. There was no injection, *exanthemata* or *exudate*.

*Throat.* Tonsils were moderately hypertrophic and moderately injected.

*Neck.* There was pronounced tenderness on attempted flexion with moderate rigidity; there was no retraction and with prolonged manipulation the chin could be pushed forward on to the chest wall.

*Chest.* Was symmetrical. Expansion was equal on both sides. No rosary.

*Lungs.* Were essentially normal throughout to auscultation and percussion; no increase in spinal or interscapular dullness.

*Heart.* Action was rapid and regular; sounds were of good quality; no murmurs or thrill made out, and there was no enlargement to percussion.

*Abdomen.* Liver was barely palpable. Spleen not made out. There were no masses, rigidity or tenderness.

*Extremities.* Were negative throughout.

*Reflexes.* Patellar jerks were not obtained. Achilles reflexes were sluggish; no Babinski, ankle-clonus or Kernig. There was a typical Brudzinski sign with some tendency toward flexion of the thigh on the trunk, with the neck as described, otherwise the deep and superficial reflexes were normal.

*Skin.* Normal.

Diagnosis of acute otitis media (bilateral) and meningitis (type undetermined) was made at that time.

Lumbar puncture was done immediately, at which time 8 cc of a distinctly turbid fluid was obtained under moderately diminished pressure. There were 2500 cells per cu. mm., 85 per cent of which were of the polymorphonuclear variety and 15 per cent lymphocytes. Globulin test was strongly positive.

Double paracentesis was performed and pus was obtained in large quantities from both ears, smears of which revealed no organisms and cultures from which gave no growth in seventy-two hours. 10 cc of antimeningococcus serum were administered at this time.

During the succeeding twenty-four hours there was no definite change in the symptoms, except that he seemed to be slightly brighter.

June 13. Second lumbar puncture was done and 25 cc of a similar fluid were obtained under slightly increased pressure. Cell count had fallen to 1100 per c.mm., of which 65 per cent were polynuclear leukocytes. Globulin test continued positive. There was no reduction of Benedict's solution. 15 cc of antimeningococcus serum were administered at this time.

June 13. The urine was yellow and cloudy. It contained albumin, large trace; sugar, 0; few red and white blood cells; no casts.

June 15. Third lumbar puncture was done and 40 cc of a similar fluid were obtained under definitely increased pressure. Cell count, 1910. Globulin positive. Benedict's solution was not reduced. 30 cc of meningococcus serum were administered at this time.

June 15. Blood: White blood count, 22,800.

June 17. Fourth lumbar puncture was done and 25 cc of similar fluid was obtained, which clotted almost instantaneously, making a cell count unsatisfactory; but there was definitely more purulent fluid than on the previous taps and the cells and organisms were increased in number.

Following the fourth lumbar puncture, which showed a decidedly purulent fluid, with a pronounced progression in turbidity, since the previous day, further lumbar puncture was thought to be futile and the treatment from that time on was symptomatic. The temperature maintained a level between 103° to 104° F. and the usual signs of meningeal irritation (Kernig, Brudzinski and neck rigidity and retraction), which were not pronounced on entry, became more marked. He grew very irrational, requiring sedatives for control. There was a marked dyspnea and the patient died on the morning of June 21, his ninth day in the hospital.

**Bacteriologic Report.** Smears of the spinal fluid made at the time of admission, and repeated four times before death, showed large numbers of both intra- and extracellular organisms having the characteristics of *Bacillus influenza*. At autopsy similar organisms were found in direct smears from the brain, cord and middle-ears. Culture of the heart's blood likewise showed them. There were no demonstrable differences between the bacilli obtained from the different organs. All grew well on blood agar but could not be grown on media without blood.

**Morphology.** The bacillus was Gram-negative and non-motile. In direct smears from spinal fluid and exudate it showed marked pleomorphism. There were many small thin bipolar staining bacilli of the so-called typical influenza type, but in addition to these there were long forms and filaments, and a thick variety (probably an involution form) which was both long and short, straight and curved. In many fields the differences in size, shape and arrangement reminded one of preparations of *Bacillus coli*. This pleomorphism persisted throughout five weeks' cultivation on artificial media and was increased by passage through a guinea-pig.

In addition to the differences present in the early smears, culture on blood agar brought out striking involution forms. Only the youngest cultures showed the morphology usually thought of as characteristic of the influenza bacillus. In from twelve to twenty-four hours there developed bizarre forms which were very thick, long and curled.

**Cultural Features.** Repeated unsuccessful attempts were made to grow the organism on plain agar, blood serum and starch agar. It could be grown only on blood agar or plain agar smeared with blood. Human blood agar proved to be a much poorer medium than that made with a guinea-pig's or a rabbit's blood. Intentional contamination of the blood plates with staphylococcus, *Bacillus*

coli and *Bacillus subtilis* did little to facilitate growth and in some cases actually inhibited it. An unsuccessful attempt was made to grow the bacillus on plain agar in symbiosis with *Bacillus coli*.

The colonies were at first of the dew-drop, pin-point variety, but after two or three days took on a slightly milky appearance. Individual colonies seldom grew to be more than 1 mm. in diameter, and were round, smooth and amorphous, with very finely irregular edges. By inoculation into starch blood agar, colonies were obtained which were 5 mm. in diameter and had slightly elevated but not lobulated edges.

*Biochemical Features.* The bacillus was non-hemolytic. It produced indol in both peptone and plain blood broth and reduced nitrates to nitrites. In brom-cresol-purple blood-broth milk there

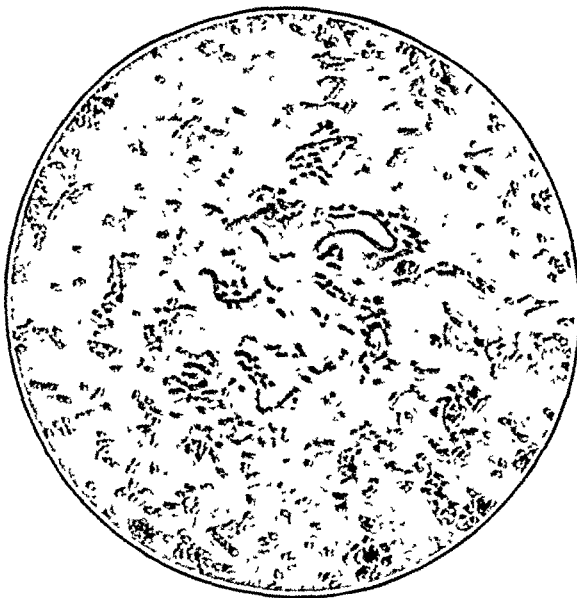


FIG. 1.—Photomicrograph (oil immersion). Twenty-four-hour culture showing involution forms grown on rabbit blood agar.

was slight but definite acidity in twenty-four to forty-eight hours, with questionable alkalinity later. It did not form amylase in starch agar media.

*Pathogenicity.* After the organism had been cultivated artificially for four weeks 4 cc of a twenty-four-hour blood-broth culture were injected intraperitoneally into a guinea-pig. The animal died in twenty-six hours and on autopsy showed an acute fibrinous peritonitis. Pure cultures of *Bacillus influenzae* were recovered from the peritoneal exudate and the heart's blood.

*Post-mortem Examination.* Autopsy was performed six and a half hours after death.

*Anatomical diagnosis:* Acute purulent leptomeningitis (*Bacillus influenzae*); internal pyocephalus with acute endymenitis; septi-



cemia (*Bacillus influenzae*); suppurative otitis media, bilateral; thromboses of the superior longitudinal and both lateral sinuses; acute bronchitis; edema and congestion of the lungs and infarctions of the lungs. The body was well developed and nourished, with unequal pupils. There was nothing remarkable in the body.

The important changes seen were in the brain. It weighed 1140 gm. and showed in addition to thrombi in the sinuses a thick greenish exudate beneath the pia mater. This was generally distributed over the lateral surfaces, most extensive near the Rolandic fissures. Here, besides filling the sulci, it extended over several convolutions, presenting patches 2 to 3 cm. in diameter. In other portions there were linear extensions of the exudate. In making cover-glass preparations the exudate was fully 1 mm. thick. It was quite firm, elastic, having practically the consistency and elasticity of a fibrinous exudate. The brain was quite plastic and the convolutions markedly flattened, the sulci being obliterated, and there was intense congestion, especially of the larger veins.

A view of the base of the brain presented a similar exudate, slightly softer, darker green and 3 to 4 mm. in thickness. It covered the medulla, pons, inferior surface of the cerebellum and an area surrounding the optic tracts, with a diameter of about 4 cm. Whereas the surface of the brain was dry on lifting it from the base of the skull and upon incising the tentorium cerebelli a large amount of thin, whitish, puriform fluid escaped from the spinal canal.

A horizontal section of the brain, exposing the lateral ventricles, showed them to be greatly dilated and containing a thick deposit of fibrinous material, especially in the posterior horns. There was destruction of the ependyma and excavation into the white matter, particularly the posterior portions. The brain as a whole was deeply injected and in the basal ganglia, especially the lenticular nucleus, the color was pink and there were apparently punctate hemorrhages. The structures bounding the third ventricle were collapsed and had probably been destroyed by the inflammatory process.

Both middle-ears contained a puriform exudate. The dura mater of the spinal cord was distended. Upon reflection the cord was covered with a thick, firm, greenish exudate similar to that seen on the cerebrum. It was about 2 mm. thick and appeared to completely envelop the cord.

**Microscopic Examination.** Many sections of the cortex and meninges show a purulent exudate beneath and distending the pia arachnoid. It consists of numerous polymorphonuclear leukocytes, many being disintegrated, a small amount of fibrin and a moderate number of large mononuclear phagocytes (endothelial leukocytes). Some of the polymorphonuclears are seen in the vessel walls. The vessels everywhere in the gray matter are distended with red cells.

In other sections there is general infiltration of the perivascular spaces of the pial vessels and those of the brain substance by numerous large, endothelial leukocytes and a moderate number of lymphoid and plasma cells.

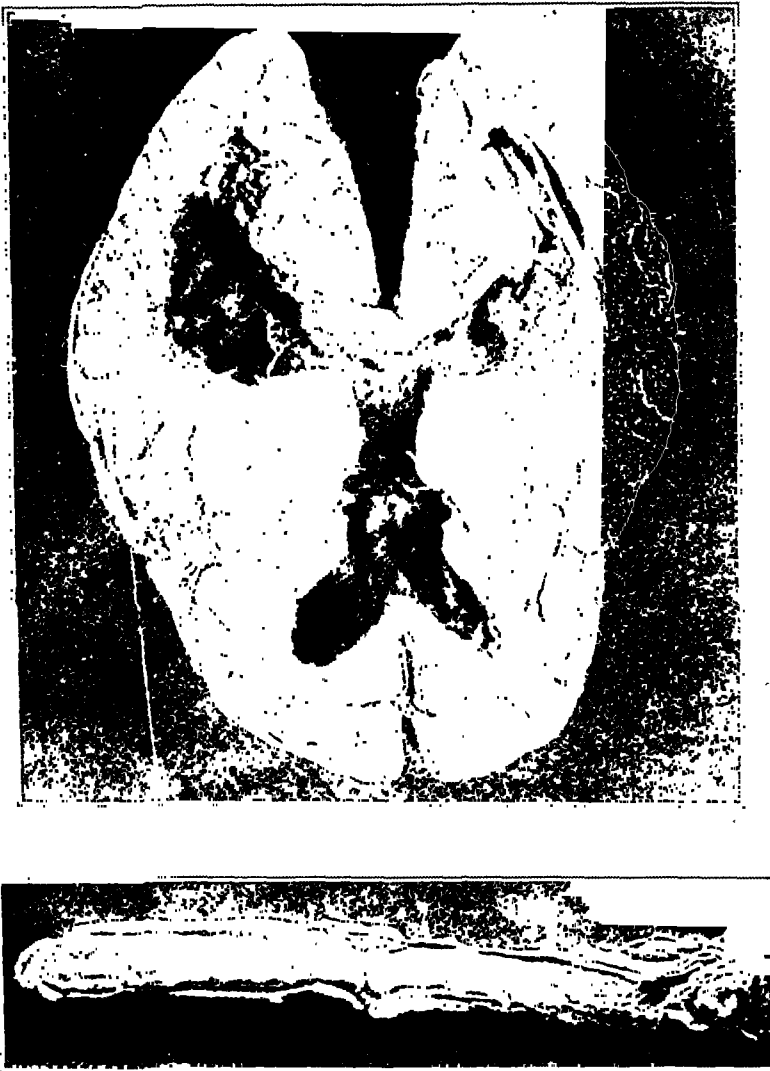


FIG. 2.—Photomicrograph of brain showing dilatation and destruction of the lateral ventricles. Below the cord is covered with a heavy exudate.

A section from the region of the lateral ventricle shows destruction, especially of the ependyma. Migrating cells are numerous, including large mononuclear phagocytes (endothelial leukocytes) many lymphoid and plasma cells, and in a few areas where the cells are vacuolated a small number of polymorphonuclear leukocytes are found. Here also there is marked perivascular infiltration. A section of the basal ganglia shows general congestion of the vessels, many being almost entirely filled with polymorphonuclears.

There is perivascular infiltration, and along one border the brain substance has a vacuolated appearance.



FIG. 3.—Photomicrograph (low power) showing purulent exudate enveloping spinal cord and nerve root.

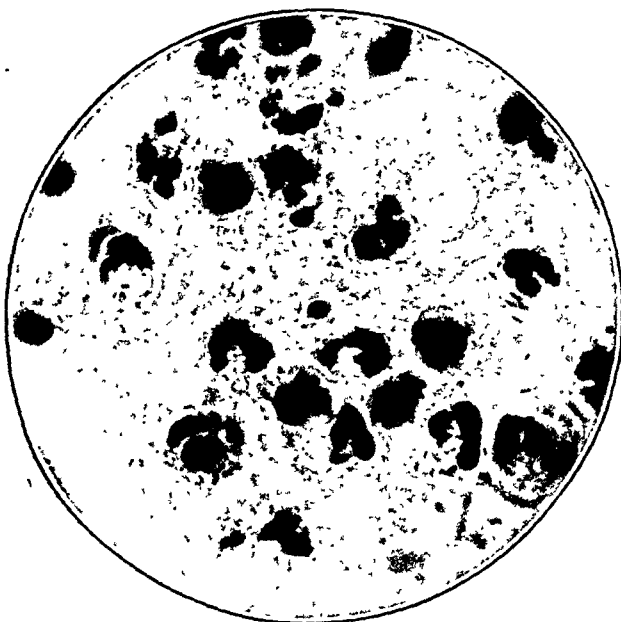


FIG. 4.—Photomicrograph (oil immersion). Smear of exudate from spinal cord showing intracellular bacilli in polymorphonuclear leukocytes.

Sections of the spinal cord show the pia mater to be distended or broken in places by a thick, purulent exudate, consisting of myriad polymorphs, many of these disintegrated and often enmeshed in heavy webs of fibrin. This exudate is extensive, involving the ventral and posterior roots as well as covering the entire cord. A Giemsa stain reveals numerous short bacilli, morphologically *Bacillus influenza*, both intra- and extracellular in the exudate.

A section of the Gasserian ganglion shows thrombi in many of the adjacent venous sinuses. The pituitary is normal.

Four sections of the lungs show extensive congestion and edema. Many of the vessels are filled with polymorphs. In two sections some of the capillaries have apparently ruptured, as shown by small patches of alveoli filled with red cells. There is a small infarct which includes about twelve to fifteen alveoli and a large vessel which is thrombosed. Many of the other alveoli are filled with a pale, eosin-staining, granular material. The lymphatics are dilated. The pleura is intact. In the bronchi there is infiltration of the mucosa by numerous polymorphs and occasional colonies of bacteria resembling chains of streptococci.

Sections of the heart, gastro-intestinal tract, pancreas, liver, kidneys and adrenals show little aside from congestion. The tonsils show slight acute inflammation.

**Summary.** The clinical picture was that of an acute meningeal infection with a positive Kernig, Brudzinski, neck rigidity, retraction of the head, fever and leukocytosis. The exact diagnosis was of necessity made through the bacteriological findings in the laboratory.

The bacillus obtained was Gram-negative, hemoglobinophilic, pleomorphic, aërobic, non-hemolytic and non-motile. Its colonies were round with finely irregular edges. Under proper conditions it produced indol, formed acid in milk, reduced nitrates to nitrites, but did not produce amylase. During five weeks of study it did not show the phenomenon of symbiosis. In a guinea-pig intra-peritoneal injection was followed by peritonitis, septicemia and death in twenty-six hours.

In its morphologic and cultural characteristics the organism so described corresponds with forms isolated from meningitis cases by Slawyk, Wollstein and others. All these investigators have emphasized the pleomorphism, but in spite of it they have, with only occasional exceptions, agreed that the organism should be classed as *Bacillus influenza*. But it has long been felt that this name was being given to a group of Gram-negative hemoglobinophilic bacilli, which might later be differentiated into strains in some such way as the streptococci have been differentiated. It was with this end in view that the various biochemical tests were suggested by Jordan<sup>14</sup> and Rivers.<sup>15 16</sup> As yet however, no constant differences have been found between the respiratory tract and meningeal organisms, and although the bacillus from the case reported in the present paper

gave characteristics similar to those shown by the meningeal strains with which Rivers worked, they do not differ in this respect from some of the epidemic strains or strains from normal throats. Up to the present time the more marked pleomorphism is the only difference noted in the meningeal form as distinguished from the epidemic strains, and we are as yet without an explanation of the fact that in the recent epidemics there were so very few cases of influenzal meningitis reported. It is still difficult to explain why, with the much more common occurrence of influenzal meningitis in infants and children a study of the complications of 816 cases of influenza in children made by Levin<sup>17</sup> at the Cook County Hospital in Chicago during the epidemic only 5 cases of meningitis should have been found, and none of these from *Bacillus influenza*.

Concerning treatment opinions differ. Torrey<sup>4</sup> summarizes the therapeutic possibilities as follows:

"I. The anti-influenzal serum of Wollstein, whose action appears to be specific. Where practicable this serum should certainly be tried.

"II. Hexamethylenamin, which has been recommended by a number of writers, notable Brem and Zeiler,<sup>13</sup> and by Batten. The latter reports a case in which recovery followed its use. There seems, however, to be less basis for regarding it of great value than is the case with either Wollstein's serum or repeated spinal puncture and drainage.

"III. Repeated lumbar puncture."

The last was first suggested by Quincke.

Added to the common pathologic picture of a purulent leptomeningitis described by Davis<sup>12</sup> there was septicemia (*Bacillus influenza*) and an internal pyocephalus with acute endyemitis.

We are indebted to Dr. W. W. Howell, from whose clinic the case was taken, and to Dr. V. C. Jacobson for the photographs.

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## EXPERIMENTAL POLYURIA.\*

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CHICAGO, ILL.

(Work done in Department of Anatomy, University of Chicago.)

THIS work was begun for the purpose of determining experimentally the effect of intravenous injections of extract of the pituitary gland upon the so-called polyuria of hypophyseal origin. Before it had proceeded far our attention was attracted to certain striking variations from the generally accepted ideas concerning the production of polyuria of this type, and it seemed worth while to investigate the means of producing it.

Dogs were used throughout all the experiments. Ether was used as the anesthetic, and during the operation was administered by the intratracheal method. The gland was exposed by the buccal (transpharyngeal) route, first described accurately and used successfully by Aschner. In each case the normal urine excretion for twenty-four hours was measured as a preoperative control. Synopsis of work:

\* This work was made possible through the kindness and generosity of Mrs. Nettie McCormick. I also wish to express my indebtedness to Dr. R. R. Bensley, of the University of Chicago, and to Dr. Dean Lewis for their interest and encouragement, and to Mr. Siegfried Maurer for his very hearty coöperation and many valuable suggestions.

1. Stimulation of the anterior and posterior lobes of the hypophysis:
  - (a) Varying degrees of heat.
    - (1) Heated rod.
    - (2) Paraffine.
  - (b) Trauma—pinching and pulling with tissue forceps.
  - (c) Cone-shaped plug of beeswax pushed into opening in bone.
  - (d) Induced current—electric.
2. Herniation of gland through dural opening.
3. Traction on base of brain with as little trauma to the gland as possible.
4. Effect of pituitrin and epinephrin on polyuria.

**Stimulation of the Anterior and Posterior Lobes of the Hypophysis with Heated Rod.**—In this group nine animals were used. After exposing the hypophysis the gland was stimulated by traumatizing it with a metal rod heated to varying temperatures. The local effect, observed post mortem, varied from a moderate hyperemia of the anterior and posterior lobes to complete destruction of the gland. In only one instance was there observed a polyuria of any considerable extent.

For eight animals of this group the average twenty-four-hour urine measured 232 cc and 221 cc for the two days immediately preceding the operation, and 200 cc, 243 cc, 253 cc, 299 cc, 277 cc, 180 cc, 260 cc and 200 cc for the successive days after the operation. This curve of urinary excretion may be seen represented graphically in Fig. 1.

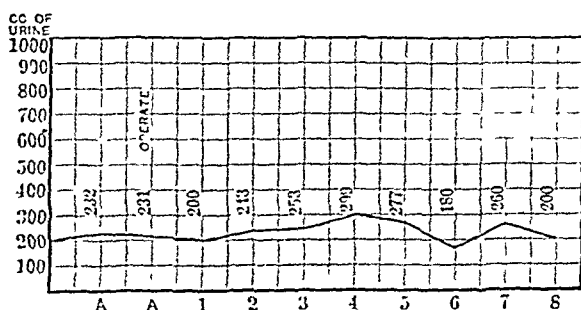


FIG. 1

In one animal of this group, dog 2, there was a marked polyuria. The daily preoperative urinary excretion was 200 cc. The stimulation consisted in trauma with a rod heated to a "black-hot" point—that is the point at which the rod appears black after cherry red has faded. The rod was 3 mm. in diameter, and was simply brought in contact with the structures at the bottom of the opening after the dura had been incised. At this stage in our work

our landmarks were not as thoroughly impressed upon us as they later were, and we were not able definitely to locate the hypophysis. During the first twenty-four hours practically no urine was voided. In the second twenty-four hours the quantity was 650 cc, and during the third twenty-four hours the amount increased to 1500 cc. At this time the dog appeared to be very sick—scarcely able to stand. It was killed at the end of the third twenty-four hours. At the postmortem examination it was found that our opening through the sphenoid bone was so far posterior that the hypophysis had not been exposed and that our stimulation had been applied to the base of the brain posterior to the hypophysis, in the region of the corpora mammillaria. The results are more conspicuously evident when shown by means of curves in Fig. 2.

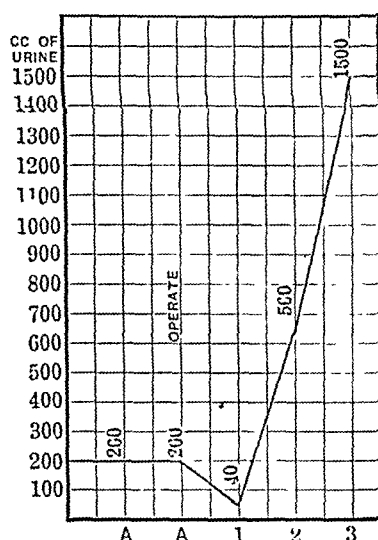


FIG. 2

**Stimulation with Heated Paraffine.**—In dogs 14, 37 and 39 paraffine heated to 70°, 110° and 130° C. was poured into the cavity in the sphenoid bone without otherwise disturbing the gland. In dog 37 the dura was not incised. In no instance was there any change in the amount of urine excreted.

**Mechanical Trauma.—Pinching and Pulling with Tissue Forceps.**—In dogs 10, 11 and 21 the gland was traumatized by pinching and pulling on the anterior and posterior lobes with tissue forceps. On the two days preceding the operation the average urinary output was 150 cc in twenty-four hours. During the twenty-four-hour period immediately after operation the average rose to 297 cc, after which it gradually fell until it reached 180 cc at the end of the fourth twenty-four-hour period after operation. This result may be seen graphically represented in Fig. 3.

**Cone-shaped Plug of Beeswax Pushed into Opening in Sphenoid.**—In dog 71a a cone-shaped plug of beeswax, approximately 1 cm. in



diameter at the base and 1 cm. long, was forced into the opening in the sphenoid against the hypophysis. The gland was tipped slightly forward so that the plug impinged on both the anterior and posterior lobes. The preoperative excretion had been averaging 250 cc to 300 cc daily. The postoperative excretion was slightly less, being from 150 cc to 250 cc daily. After ten days of observation the dog was apparently in normal physical condition and was used for other experimental work.

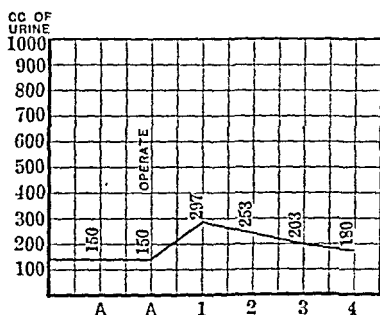


FIG. 3

**Induced Electric Current.**—The gland was stimulated by means of an induced current in dogs 58, 63, 66, 69a and 70a. In each instance there was an increase in the daily amount of urine. This was most marked in dog 63. During the two days preceding the operation in this experiment the urine excreted in twenty-four hours measured 300 cc. Following electric stimulation the amount increased to 1400 cc in the first twenty-four hours, 3800 cc in the second twenty-four hours and 4200 cc during the third twenty-four hours. This polyuria lasted for six days, but as the urinary output was modified by other experimental work for which the animal was used, the remaining period will be discussed later. Fig. 4 indicates graphically the extent of this change.

**Herniation of the Gland through the Dural Opening.**—In dog 15 the sphenoid bone was much wider than is usual and the venous sinuses surrounding the hypophysis were correspondingly formed in a larger circle. This made wider incision of the dura possible. When this step of the operation was performed the gland herniated through the dural opening, forced by a gush of cerebrospinal fluid. The degree of protrusion of the gland and the amount of cerebrospinal fluid were greatly in excess of anything previously noted. No manipulation was necessary to bring the gland well into view. A small portion of the anterior lobe was excised and the operation stopped. The dog was in excellent condition at the close of the operation. The urinary output during the three days previous to operation was 160 cc per twenty-four hours. This increased to 2360 cc during the first twenty-four hours and to 3680 cc during the

second twenty-four hours following operation. It then fell to 2140 cc in the third twenty-four hours. The dog was in excellent condition, but was killed at this time in order that the tissues might be studied during active polyuria. The excretory curve on dog 15 is shown in Fig. 5.

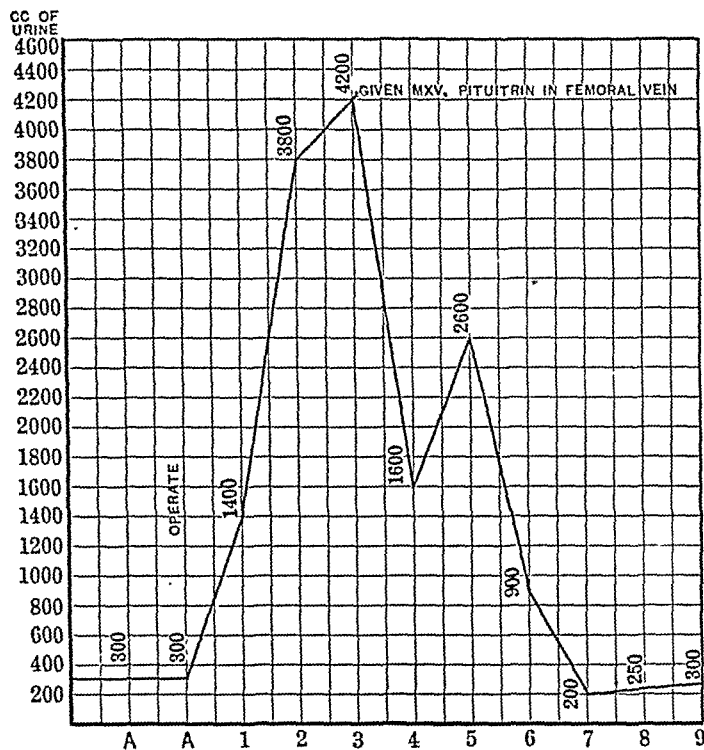


FIG. 4

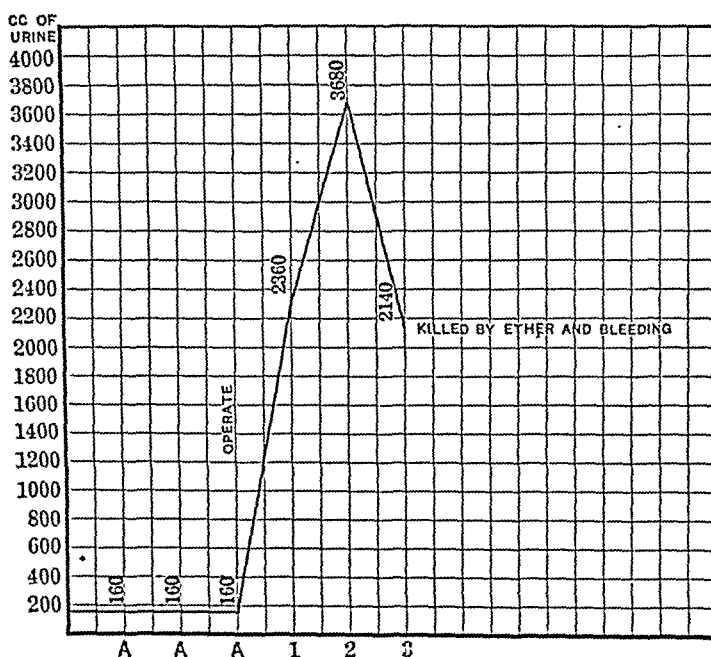


FIG. 5

Dog 28 was operated in the usual manner and in this instance also the gland was forced through the dural opening by the intracranial pressure. This herniation was not so marked as in the former case. Slight traction was made on the stalk, but an effort was made to avoid injury to the gland. The urine voided during the two days preceding operation measured 90 cc and 100 cc. During the first postoperative twenty-four hours 900 cc of urine were voided (Fig. 6). The quantity decreased to 200 cc during the second twenty-four hours. At this time this animal was in such bad condition that it was released from its cage. It died the following day. Postmortem examination showed no evidence of meningitis. The cause of death was bronchopneumonia. On the basis of these two observations a group of twenty dogs were operated.

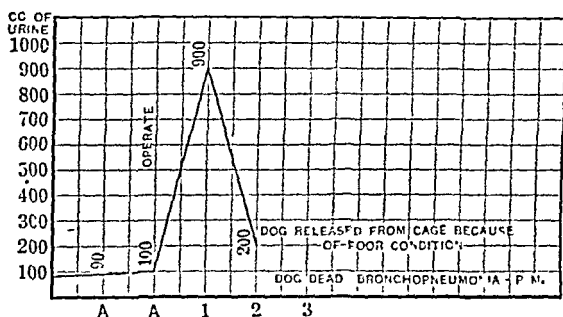


FIG. 6

**Traction on the Stalk and Base of the Brain with as Little Injury to the Gland as Possible.**—In these animals an effort was made to avoid trauma to the gland itself while making traction on the stalk and its attachment to the floor of the third ventricle. The traction was made by introducing behind the gland a pair of dental cotton-holding forceps, the points of which extended forward beneath the pars nervosa. The stalk was grasped as gently as possible and the traction made through it on its attachment.

The complete result of this entire group may be summarized as follows: Average preoperative excretion in twenty-four hours for the two days immediately preceding operation, 145 cc; postoperative excretion for each twenty-four hours: First, 893 cc; second, 1003 cc; third, 857 cc; fourth, 628 cc; fifth, 807 cc; sixth, 907 cc; seventh, 300 cc; eighth, 200 cc; ninth, 150 cc. Fig. 7 shows the composite result graphically.

The most marked polyuria of this group occurred in dog 55 (Fig. 8). In this animal the output increased from 200 cc on the days preceding operation to 4000 cc during the second twenty-four hours after operation. This dog was allowed to live six days and was in good condition when killed. Postmortem examination showed a hemorrhage into the third ventricle. The hypophysis

showed no gross changes other than a plastic exudate filling the defect in the sphenoid and covering the anterior lobe of the gland.

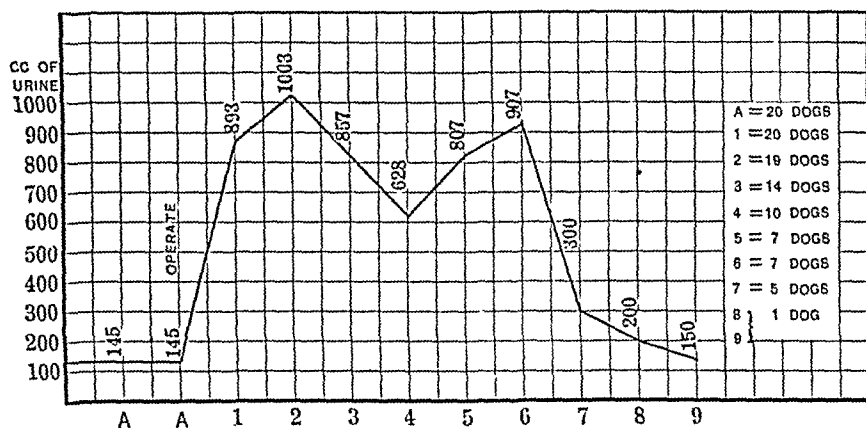


FIG. 7

It will be noted that the entire number of the dogs in this group were not allowed to survive the full period of their polyuria. It will also be observed that the average urinary excretion on the third, fourth and fifth days fell below the average for the second and the sixth day. This work was not for the study of the type and duration

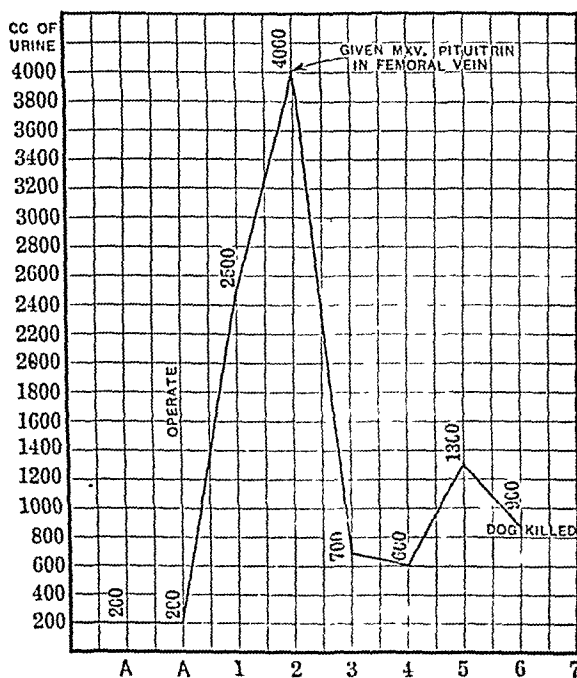


FIG. 8

of a polyuria induced by stimulation in the region of the hypophysis. Therefore, after the highest point in excretion had been reached,

or at least such a point as could be definitely regarded as a polyuria, many animals were used for supplementary experiments. Some were killed to secure tissue at the height of urinary excretion for cytologic study. Others were used to observe the effect of pituitrin and epinephrin on polyuria produced by stimulation in the region of the hypophysis.

**Effect of Pituitrin upon Experimentally Produced Polyuria.**—A group of six dogs (55, 56, 58, 59a, 63 and 64) were given pituitrin intravenously after polyuria had been produced. In every instance there was a marked decrease in the urine excretion in the twenty-four hours following the injection. In three of the animals (55, 59a and 63) there was a secondary rise in the excretory curve after the effect of the pituitrin had passed. This was then followed by a more gradual decline to the preoperative level. This is shown graphically in Fig. 4 and Fig. 8.

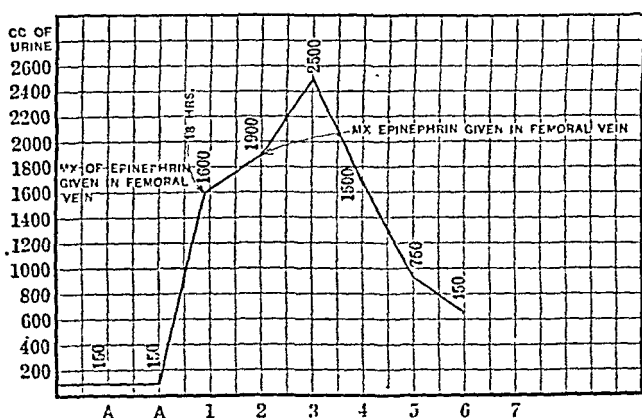


FIG. 9

**Effect of Epinephrin upon Experimentally Produced Polyuria.**—Five dogs (67, 69, 69a and 70) were given varying amounts of epinephrin intravenously after the establishment of a polyuria. Two of these dogs were given a second dose twenty-four hours after the first injection. In no instance was any change in the rate of excretion noted which could be regarded as the effect of the gland extract. In Fig. 9 the excretory rate in one of these animals is represented graphically.

**Discussion.**—The evidence dealing with the etiologic factors involved in the so-called "polyuria of hypophyseal origin" is conflicting and confusing.

That a polyuria is frequently associated with lesions in the sella turcica, involving to a greater or lesser degree the hypophysis, has been recognized clinically for many years. Hagenbach, in 1882, described a case of tuberculous meningitis—a caseous nodule in the infundibulum, dilated lateral and fourth ventricles—associated with

a marked polyuria, in a child aged four and a half years. Borelli, Meyenburghs, Haushalter and Lucien and others have reported similar processes, but with greater destruction of the gland. In one of Meyenburghs's cases only a small fragment of the anterior lobe remained.

Metastatic tumors in the pituitary gland associated with polyuria have been reported by M. Simmonds, H. Rosenhaupt, Sekiguchi, Kennaway and Mottram, Erdheim, Cushing, Fleckseder and others. In these cases the changes in the gland varied from a complete destruction to an involvement limited to the stalk alone (Cushing). In the 10 cases collected and reported by Simmonds, however, only 3 showed urinary increase. Of the remaining 7, 2 were described in some detail. In the first the pars nervosa, pars intermedia and infundibulum had been replaced by the tumor mass. In the second the entire gland, except a small part of the anterior lobe, had been destroyed by tumor. Neither of these cases was associated with any increase in urine excretion. Eason and Johnson and Strada and others describe similar cases in which the pars nervosa, pars intermedia and infundibulum are replaced completely or incompletely, in which no mention is made of polyuria.

A. Berge and Schulman have recently reported a case of diabetes insipidus which at postmortem examination showed gummatous lesions in the hypophysis, especially involving the pars nervosa. In this case the polyuria subsided temporarily when given extract of the posterior lobe.

E. Frank has reported a marked polyuria following the penetration and lodgment of a bullet in the sella turcica. He emphasizes the opinion that mechanical and thermal injury to the exposed gland may cause a long-continued polyuria, and concludes that this is due to the irritation of the pars intermedia.

The frequent association of diabetes insipidus with head injuries, especially fracture of the base of the skull, has been pointed out by Borszaky, Cushing, Kleeblath, Finkelnburg, Graham, Nothnagel and others, and has been attributed to injury of the pituitary gland. Cushing observed an "unaccountable postoperative polyuria of extreme grade" in a number of his surgically treated cases. In 1 case, a struma with moderate signs of hypopituitarism and a normal urinary output, there developed an extreme diabetes insipidus following a simple sellar decompression.

Polyuria has also been frequently noted associated with dwarfism, acromegalia and dystrophia adiposa genitalis, and upon roentgen-ray examination changes in the contour of the sella turcica have been noted.

Kahler, Bruns, Oppenheim, Ebstein, Pichler and others have recorded polyuria associated with various lesions of the base of the brain, including tumors of the third and fourth ventricles, the posterior perforated space and corpora mammillaria, syphilitic

processes in the region of the floor of the third ventricle, etc. In none of these cases, however, was involvement of the hypophysis excluded. Nor is it an easy matter to estimate the effect of such slight changes as occurred in the case of diabetes insipidus, reported by Götzel and Erdheim, in which the only variation in the hypophysis was a slight flattening as a result of pressure from a tumor of the third ventricle. Such a slight modification, as the cause of a marked polyuria, is difficult to reconcile, on a hypophyseal basis, with such cases as are reported by Cushing, in which, due to non-hypophyseal intrasellar tumors, the hypophysis is greatly flattened and distorted without change in the excretory rate.

From this very cursory review of the clinical aspect of this problem, though left in apparent confusion, it seems reasonable to conclude that:

1. Polyuria is not always associated with an increase in the activity of any part of the hypophysis, since it is seen with almost complete destruction of the gland.

2. Polyuria is not always associated with a decrease in the activity of any part of the gland, since almost complete destruction of the gland is seen without any change in the excretory rate.

Experimental work on polyuria dates from the classic work of Claude Bernard in 1849. He produced an increased urine excretion by injury to a point in the floor of the fourth ventricle anterior to his diabetic pig<sup>ure</sup>. Later, Eckhard verified Bernard's results and added several regions in the brain, stimulation of which produced polyuria. Kahler working on rabbits was able to produce a permanent polyuria closely resembling diabetes insipidus in man. By injecting small quantities of concentrated silver nitrate solution into various parts of the brain he was able to cause a polyuria accompanied by polydipsia, both lasting several weeks. The areas, injury to which were most likely to produce polyuria, were the corpus trapezoides of the pons and the lateral part of the exposed portion of the medulla. From the work of these investigators it would appear that a polyuria can be produced in dogs and rabbits by injury to the floor of the fourth ventricle, by lesions in the different parts of the middle lobe of the cerebellum and by injuries to the posterior part of the pons.

Of the more recent work that of Paulesco and Aschner stands out most prominently, as they first described and used successfully the two methods of exposure of the hypophysis which, with certain modifications, are the only two routes used at the present time. The transtemporal route of Paulesco, modified somewhat, is the method used by Cushing and his co-workers. Regardless of the operative procedure on the gland, the effect on urinary excretion in their various reports was inconstant. Polyuria was observed more frequently in those animals in which a silver clip was applied to the stalk and in subtotal removals with subcortical transplants than in any other groups. Homans, however, working on cats,

studying the effect of total removal and using the buccal route, observed polyuria in every instance. His method of removal of the gland was to grasp it by the stalk and pull it out. The removal was not complete in every instance, but in each case he produced a marked increase in the daily urinary output. Cushing also observed that the incidence of polyuria was greater in operated pups than in adult dogs. Though excellent in every particular of technic it seems quite possible that in all of this experimental work, one factor, though mentioned, was underestimated—that of traction upon and injury to the floor of the third ventricle. Due to the smaller available space in pups the lateral and upward displacement of the brain must be relatively much greater to gain an exposure equal or approaching that of a larger animal. It would produce a much greater amount of traction on the gland, stalk and its attachment.

The buccal or transsphenoidal method of approach of Aschner, which was the one used in this work, is also subject to certain objections. The certainty of a definite amount of infection, the danger of hemorrhage and the inaccurate estimation of stimulation or trauma inflicted to the gland and adjacent structures are the more important ones.

In this work it may be said only one animal showed any evidence of infection other than the slight plastic exudate over the exposed portion of the anterior lobe. In this case a cotton pack was inserted at the operation to fill the opening in the sphenoid bone. In all others the opening was left wide open and thus maintained free drainage into the mouth. By care we were able to avoid hemorrhage.

While it was impossible to regulate accurately the degree and extent of injury inflicted to the gland and its neighboring structures, we found no urinary increase of any consequence in any animal in which either the anterior or posterior lobes individually or the entire gland were stimulated by non-diffusible means, *i. e.*, heat or mechanical trauma. Stimulation of the hypophysis with an induced current produced polyuria. However, as an electric stimulus may be transmitted over a considerable distance it cannot be said that this trauma is limited to the gland itself or that the resulting urinary increase is of hypophyseal origin.

By traction on the stalk with an effort to avoid trauma to the gland itself we were able to produce polyuria regularly. We were able also to regulate roughly the degree of this increase—moderate or extreme—by modifying the amount of trauma (traction) exerted. Other animals operated, in which the same procedure was followed except for traction on the stalk, showed no or only slight polyuria. It will also be observed that in those experiments in which the hypophysis was mechanically stimulated the injury to the gland was greater than that inflicted in the process of making traction on the stalk. In the former the average daily preoperative output of



150 cc was increased to 297 cc in the first twenty-four hours and then gradually decreased, reaching normal in four days. In the latter the average daily preoperative excretion of 145 cc was increased to 893 cc in the first twenty-four hours and 1003 cc in second twenty-four hours after operation. It remained high and did not reach the preoperative level until the ninth day.

The three outstanding experiments to which we desire to call special attention are animals 2, 15 and 55. In the case of dog 2 the opening in the sphenoid was made so far posterior that the hypophysis was not exposed and the stimulation (cauterization) was applied to the region of the corpora mammillaria. In dog 15, due to peculiar anatomic arrangements, the gland came through the dural incision with considerable force, followed by a larger amount of cerebrospinal fluid than had been usually observed. Except for these variations there was nothing done which had on previous occasions produced more than a negligible increase in the urinary excretion. In dog 55 there was found at postmortem examination a hemorrhage into the third ventricle. This animal was operated in the series in which traction was made on the stalk and its attachment to the base of the brain. The associated polyuria was the most marked of the series.

In these three animals we see, in addition to a conspicuous increase in the urinary output, evidence of what quite possibly is the active etiologic factor. In dogs 2 and 55 there was gross evidence of injury to the base of the brain (the region of the floor of the third ventricle). In animal 15 the force with which the gland herniated through the dural opening may be considered to have produced trauma of the same sort, but not appreciable *macroscopically*. This is in accord with the results of Camus and Roussy, published in 1914.

**Conclusions.**—1. Clinical evidence, though indefinite, indicates that neither increased nor decreased activity of any portion of the hypophysis is uniformly associated with polyuria.

2. Experimental lesions of the hypophysis itself are not constant in the production of polyuria. Some additional element is the determining factor.

3. Experimental lesions of the hypophysis, similar to those producing negligible excretory changes, when associated with traction upon its attachment to the floor of the third ventricle uniformly produced polyuria. The degree of polyuria was roughly in proportion to the amount of traction.

4. Polyuria associated with hypophyseal changes is due to stimulation of the regional base of the brain, floor of the ventricle, corpora mammillaria, etc.

5. Intravenous injections of pituitrin temporarily lowered the excretory rate in a polyuria thus produced.

6. Intravenous injections of epinephrin have no effect on polyuria of this type in dogs.

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## THE CORRELATION OF CLINICAL AND PATHOLOGICAL FINDINGS IN NEPHRITIS.

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THE idea that clinical findings in nephritis and laboratory results do not agree, and that the lesion in the kidney cannot be interpreted in terms of function, has been long current among physicians. This mental attitude toward the problem is quite generally, if unconsciously, assumed at the bedside and undoubtedly does harm on

the whole by tending to make the management of individual cases too much of a group matter without due regard to evaluating, as far as possible, the function of each part of the kidney mechanism and treating the particular patient accordingly.

Widely different clinical manifestations are grouped together as nephritis, or some substitute term, such as nephrosis or nephropathy, is used. The child, who during an attack of scarlet fever becomes dropsical, passes a small amount of urine of high specific gravity, rich in albumin and casts, without retention of nitrogen in the blood, and with perhaps little increase of blood-pressure, is said to have "nephritis." At the other extreme of the series we find the man past middle life who has no anasarca, who passes abundant urine of low specific gravity, with perhaps the faintest trace of albumin and a few hyaline casts, and who presents marked signs of nitrogen retention and increased blood-pressure.

We know that these two conditions, and many others with varying clinical pictures lying between these two extremes, are due to disturbances of kidney function which result from injury to the kidney and its attendant reactions of repair. We do not know, in most cases, exactly what caused the injury and are prevented by lack of this knowledge from classifying them etiologically.

Two entirely redundant, and for the most part meaningless, terms have crept into the literature. These are "nephropathy" and "nephrosis." The latter has no etymological excuse for existence and the former means "any disease of the kidney." The words nephropathy and nephrosis have been used by most writers to designate injury to the kidney without attendant inflammatory reaction, or injury to the kidney, with consequent fibrous change, without an acute inflammatory stage, as evidenced by exudate, and migration of cellular elements. If it were generally agreed among pathologists that only those processes attended by exudate and round-cell infiltration should be termed inflammations the above words might be used as substitutes. It seems better to the author not to tamper with our present conception of the nature of the inflammatory process and to consider the matter from a broad biological point of view.

Any living tissue when injured by any agency whatsoever is subject to a series of phenomena which have as their basic biological purpose the repair of the injury. These changes, taken together, no matter in what stage of the process they are observed, constitute inflammation (Adami, Warthin).

We can conceive that we may view the tissue so soon after the injury that we cannot detect any reaction by our usual methods of examination, or we may view the tissue so long after the reaction is complete that we see only the scars left behind by the attempts at healing. There is no sharp line of demarcation between any of these stages, and different noxa are reacted to in quite different ways;

therefore it is quite academic, as well as wholly impracticable, to split off "nephroses" and nephropathies" in our classification and separate them from the "nephritides."

The kidney may be considered, for purposes of study, as consisting of a glomerulus with a system of tubules and their attendant blood supply.

The primitive metazoa lived in the sea and had a very simple problem of excretion presented to them. These animals had an abundant supply of water and salts at their command at all times. They could filter through their primitive segmental nephridia several times their weight of water in twenty-four hours and needed no mechanism for the conservation of salt. Therefore, there was developed in them the simplest kind of a filter by which the catabolites, resulting from their life processes were diffused into the surrounding sea from their celomic cavities. This primitive filter is the analogue of the glomerulus which later becomes attached to or rather invaded by a vascular tuft; but the glomerulus retains down to man himself the primitive function of a simple filter and nothing more.

The next problem which was presented to the kidney mechanism resulted when the marine animal became a fresh-water animal or fresh-water amphibian. In these cases water was still present in abundance, and more than the animal's weight in urine could be secreted in twenty-four hours; but the valuable salts were no longer present in the liquid and had to be conserved. Thus the kidney tubule was developed, primarily, as a mechanism to conserve salt and resorb these radicals as the glomerular filtrate passed on its way to the excretory opening.

As animals became more terrestrial in their habits a new necessity arrived in the shape of a demand for water conservation. It was no longer expedient to drink the large amount of water necessary to dispose of catabolites through a simple filter. In the case of the human animal it would be necessary to drink a wholly impractical amount of water if the catabolites were to be removed as simple filtrates through the glomerular mechanism. An example makes this clear. There are 30 mg. of urea in 100 cc of blood, or 0.3 gram per liter. In order to get rid of 20 grams of urea in twenty-four hours, 67 liters of water would have to be filtered through the glomeruli. In order to pass 67 liters of urine the animal would have to drink at least that much water, which would again amount to as much as the individual's weight.

Before the vertebrate stage evolution had already developed the tubular mechanism for resorbing such salts as were necessary from the glomerular filtrate, and to this function of the tubule the function of resorption of water was added. By resorption of water by the tubules as the glomerular filtrate passed to the exterior the animal might use his water over and over again and avoid drinking

or passing in the urine such excessive quantities; but still the filtration through the glomerulus of such large quantities of fluid would be a wasteful process requiring the specific and selective resorptive function on the part of the tubule of a very large quantity of material. Thus the last and most important function of the tubule was developed—namely, the function of actively secreting waste nitrogen. This allowed the quantity of glomerular filtrate to be cut down remarkably, and the mammalian kidney tubule as found at the present stage of development performs a threefold function, which functions have probably been imposed upon it in the course of evolution in the following order:

1. Selective resorption of salts.
2. Resorption of water with resulting concentration of the urine.
3. Active secretion of waste nitrogen (urea, uric acid).

The glomerulus as above stated acts as a simple filter and probably filters in the neighborhood of 6 liters of water into the tubular mechanism each twenty-four hours. Of this 6 liters the tubules usually resorb about  $4\frac{1}{2}$  to 5 liters. The urine is thereby concentrated and the salts necessary to the organism are selectively resorbed. While the glomerular filtrate is passing down the tubule the waste nitrogen (urea, uric acid) is secreted by the tubule into the lumen and added to the glomerular filtrate.<sup>1</sup>

In general it may be said, then that the secretion of water and salts depends upon glomerular function and the ability of the kidney to concentrate the urine, to conserve necessary salt radicals and to eliminate nitrogen depends upon the tubule function. We should therefore expect to find, when considered from a functional point of view, four main groups of nephritics:

1. Diffuse glomerular injury preponderating.
2. Diffuse tubular injury preponderating.
3. Focal (spotted) embolic lesions producing acute inflammatory reaction in circumscribed areas, with the majority of the kidney cortex free to carry on function.
4. Diffuse fibrous kidney, which by reason of arteriosclerosis or of some other slowly acting unknown cause has destroyed both glomeruli and tubules to an extent such as to embarrass function. This class is made up of the so-called cases of interstitial nephritis and late stages of Group 3.

The author does not claim that each of these groups is always clear cut, and distinctly separate from the others, but believes that almost pure examples of each type are readily found if looked for. Further, when in acute cases death occurs before secondary and additional injury sets in from complicating factors the lesion found microscopically usually is the one expected, if the symptoms and

<sup>1</sup> For a full discussion of the mechanism of kidney secretion, including the literature, see Baylis, W. M. (Principles of General Pathology, Longmans Green & Co., 1915) and Cushman, A. R. (The Secretion of Urine, Longmans, Green & Co., 1917).

signs have been interpreted in the light of the functional mechanism above set forth.

The following examples illustrate each group:

1. Acute Diffuse Glomerular Injury.

If our present belief that the glomerulus is a simple filter, having primarily to do with elimination of water and salt is correct, we should expect that any noxa injuring the glomeruli diffusely, but leaving the tubule relatively uninvolved, would have the following effect:

- (a) The quantity of urine and the salt output would be decreased.
- (b) There would be salt and water retention with general anasarca.
- (c) The nitrogen elimination would go on uninterrupted as long as there was sufficient urine secreted to wash it down the tubules. This would be the case as long as the glomerular injury was purely or for the most part capsular; but if the vascular tufts became thrombosed or blocked off by the pressure of capsular exudate then the tubules would be deprived of blood supply and would partake of the injury.

(d) The injury to the glomerulus allows the escape of large quantities of albumin.

The clinical manifestations which we should expect of an acute nephritic with a pure glomerular injury are as follows:

- (a) General anasarca with chloride retention without high blood nitrogen.
- (b) Small amount of urine in twenty-four hours, of high specific gravity and abundant albumin and casts.
- (c) A blood-pressure which becomes progressively elevated as the glomerular function fails and falls as soon as the glomerular function is reestablished.

A photomicrograph of the lesion in the kidney from such a case is appended (Fig. 1). It will be noticed that the glomerular capsule is filled with a cellular exudate and that the tubular system is apparently uninjured.

The question of the management of these cases is an important one. The indications to be met are the low urinary output, the anasarca and the marked albumin loss. These patients develop a severe anemia rather rapidly, probably due to the albumin loss. The loss of large quantities of albumin with consequent lowering of the colloidal pressure of the serum and a relative hydremia has never been sufficiently investigated as a cause contributing to the anasarca of nephritis. The pure or nearly pure glomerular type of diffuse nephritis—that is, the type with high albumin loss without nitrogen retention in the blood—is the one in which the best results are to be expected from Epstein's high protein feeding.

As to whether salt is primarily and specifically retained, or whether it is merely retained because water cannot filter through the glomerular membrane, is still unsettled. Most authorities believe that

salt is retained primarily and edema develops in nephritis because of salt retention in the tissue. The evidence in support of this idea is entirely insufficient for it to be considered proved or even presumptively established. As a matter of fact, in the vast majority of cases water and salt are retained together, and for the same reason—namely, that the filter is clogged. The salt is not excreted because the water is not excreted, and when the kidney becomes capable of eliminating water, salt is no longer retained.

The disciples of the primary salt retention doctrine point out that if salt be removed from the dietary the patient loses his edema. When this is the case (and everyone knows that often edema, demon-

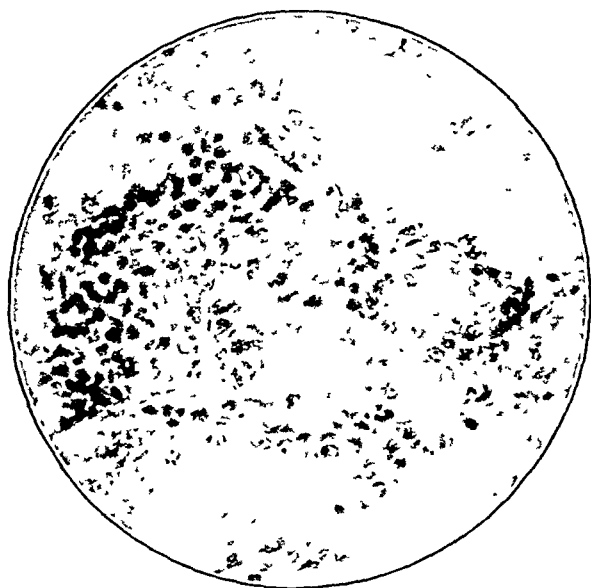


FIG. 1.—Acute glomerular nephritis. Capsular space filled with exudate. Tubules relatively normal.

strably nephritic and not cardiac in origin, remains in spite of the removal of salt from the dietary) it is due to two and possibly more factors. The first of these is that any edematous patient when deprived of salt automatically drinks a minimum amount of fluid. The writer has repeatedly verified this point by observation of the fluid intake without the patient's knowledge or any suggestion regarding the amount of water taken. The balance in this way is often restored and the kidney is able to gradually gain on the edema. It is also quite well known that there is a wide difference in the facility with which electrolytes pass through colloidal membranes and an injured glomerulus may well have its permeability to sodium chloride lowered without water permeability being seriously inter-

fered with. Of course, this latter explanation is simply the primary salt retention notion in another form.

For a certain small percentage of cases with edema it seems as though such a hypothesis must be entertained because we occasionally see patients with nephritis associated with edema who will get rid of their anasarca as soon as we restrict salt in spite of the fact that fluid intake is kept up even as high in some cases as 1800 cc in twenty-four hours.

## 2. Acute Diffuse Tubular Injury.

If the tubular epithelium were uniformly and diffusely injured, leaving the glomeruli and blood supply intact, we should expect glomerular function to be preserved and tubular function to be

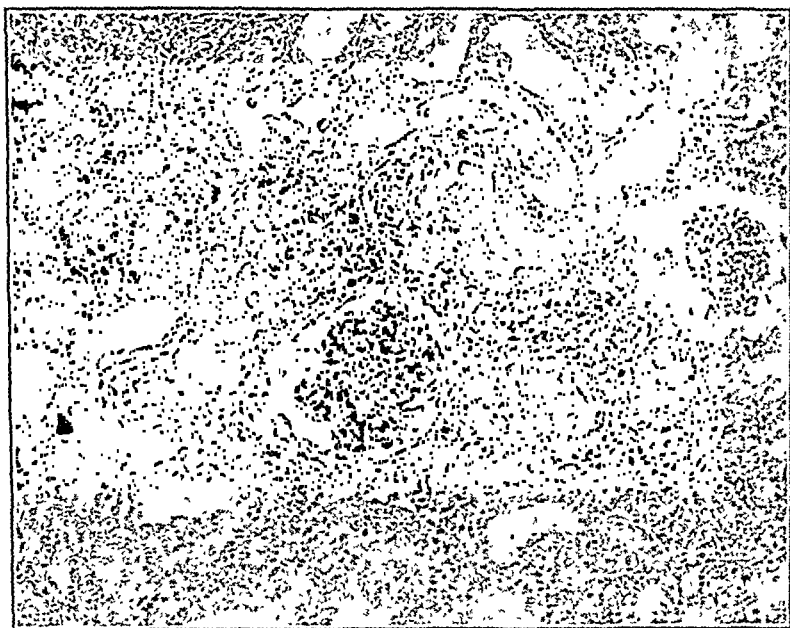


FIG. 2.—Mercuric chloride poisoning. Tubule injury of moderately severe degree.

interfered with proportionately to the degree of injury. In this case we shall expect:

(a) Normal (or increased) urinary output without salt retention or edema.

(b) Urine of normal or low specific gravity with a varying amount of albumin depending on the degree of the injury.

(c) Retention of urea, uric acid and finally creatinine with or without so-called uremic manifestations, such as gradually deepening confusion, coma or convulsive seizures.

The best examples of this type are the cases of mercuric chloride poisoning, two of which with different degrees of injury are shown in the appended photomicrographs (Figs. 2 and 3).

Neither of these patients developed anasarca. The total salt and fluid output remained normal. The sediment contained many epi-



thelial and granular casts. There was a progressive rise of the blood nitrogen until death. Another patient with mercuric chloride poisoning, who recovered, secreted from 1200 to 1700 cc of urine throughout her stay in the hospital, although the total non-coagulable nitrogen rose to 237 mg., and she was delirious for several days. The salt output was normal and no anasarca developed.

The incidences illustrate very well the effects of a diffuse tubular injury, rapidly produced, without glomerular involvement.

The relation of tubular injury to so-called uremia is of interest, but incapable of fruitful discussion at present. It is a fact that cases clinically "uremia" have anatomical evidence of tubular injury and have the blood chemical findings of depressed tubule function. On the other hand it is well known that absolute inhibition of kidney

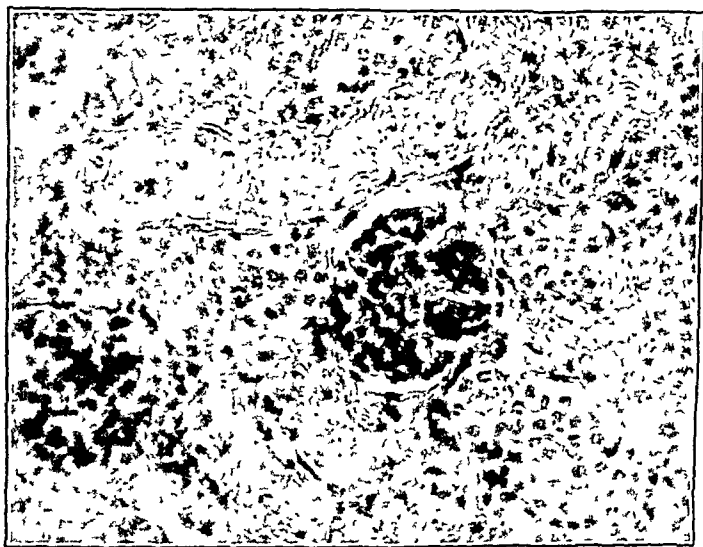


FIG. 3 —Mercuric chloride poisoning. Complete destruction of tubular epithelium, coagulation necrosis

function, such as obstruction of both ureters, is not clinically attended by uremic manifestations, although the blood chemical findings point to a complete retention of substances secreted by the tubules. Some authors (Foster) have attempted to show that "convulsive" uremia differs from the ordinary type in that methyl guanidine or related substances are found in the urine, and it has been suggested that the convulsions have been due to the presence of these substances. The assumption is of the *post hoc propter hoc* variety, and before it is assumed that the convulsions are due to methyl guanidine or its congeners it should be recalled that creatine and creatinine, which are derivatives of methyl guanidine, are substances closely related to muscle catabolism, and the above-mentioned bases may be rather the result of the convulsions than their

cause. The author believes that the manifestations grouped together clinically under the head of uremia are the result of brain edema of varying degrees and distribution, and that nitrogen retention and uremia, while clinically coincident, are not necessarily etiologically related. In this connection it is of interest to recall Martin Fisher's belief that amines may cause edema as well as acids and alkalis. The view that uremia is related to brain edema is one of the earliest that was offered. Ludwig Traube, in 1848, so explained it, and the idea has recently been revived. In the author's experience with a large autopsy material, wet brain is the most constant autopsy finding in patients dying of "uremia." Some time ago we pointed out the importance of estimating the preformed ammonia in the spinal fluid of these patients.

The occurrence of acute diffuse glomerular nephritis and acute diffuse tubular nephritis as distinct clinical entities is not uncommon. The glomerular type occurs oftener than the pure tubular, and still more often a glomerular injury progresses until the tubule partakes of the damage and we have functional evidence of a true diffuse nephritis with both glomerular and tubular malfunction. The best example of tubular injury is found in acute mercuric chloride poisoning. Here the continued normal output of water and chlorides, with marked retention of nitrogen and "uremic symptoms," taken with the postmortem findings, as shown in the photomicrographs, make a clear case of tubule injury. We also meet with certain cases of the kidney of pregnancy which appear to have primarily a tubular injury usually coupled with exacerbations of true diffuse nephritis with accompanying glomerular injury.

### 3. Embolic or "Focal" Injury.

The third group is most interesting and embraces a large number of the cases of so-called "acute nephritis" or "recurrent acute nephritis" and "subacute chronic parenchymatous nephritis." These are the cases which result from multiple embolic involvement from focal infection elsewhere in the body. The photomicrographs from two cases of this type, one recent and acute and one of longer duration, are shown in Figs. 4 and 5. The nature of the lesions here makes it plain that areas of intense inflammation and tissue destruction are simply distributed in a spotted fashion throughout an otherwise normal cortex.

These cases in their early stages are characterized by the fact that they show marked evidence of kidney lesion, as judged by albumin and casts and even blood in the urine; but their kidney function, judged by blood chemistry, urinary output, salt elimination and blood-pressure, is normal or quickly becomes normal after the first few days in bed. The explanation of these findings is, of course, evident in that we have ample normal kidney parenchyma functioning in between the involved areas. The products of the inflammatory reaction and the results of the injury, albumin, casts

and blood are found in the urine. These come down from the involved areas. The rest of the kidney is normal and functions

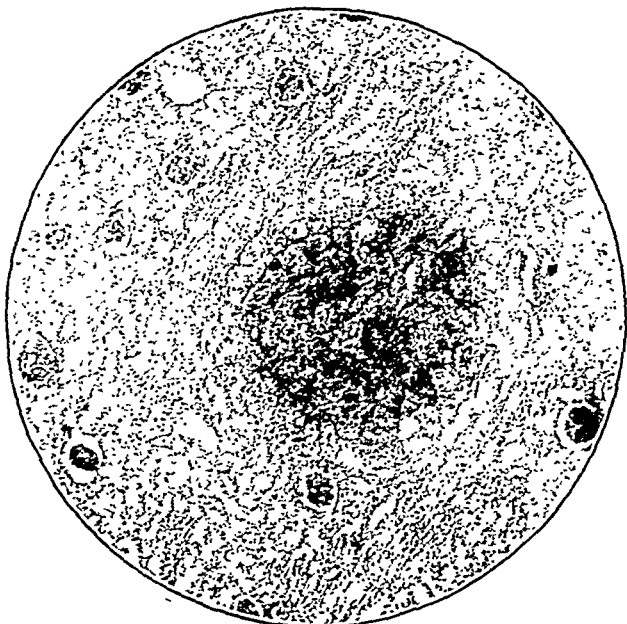


FIG. 4.—Embolic (focal) nephritis. Recent lesion. Area of acute inflammatory reaction surrounded by normal kidney tissue.

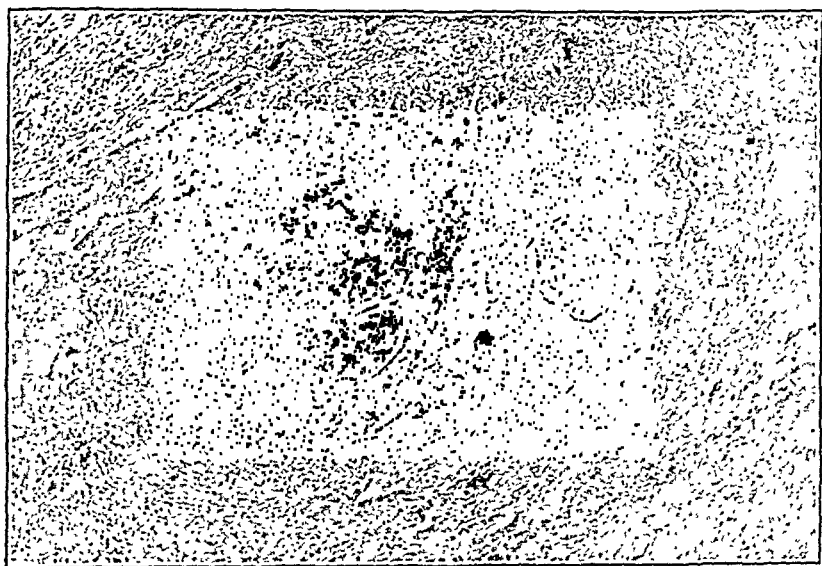


FIG. 5.—Focal nephritis. Recent (subacute) lesion in the course of a chronic embolic nephritis.

normally so that we do not find nitrogen, water or salt retention; and high blood-pressure does not supervene until late, when so much parenchyma has been destroyed piecemeal as to leave insufficient cortex to perform normal function.

These cases are subject to acute recrudescence usually at times of exacerbations of their focal infections. At these times they may present signs of temporary embarrassment of kidney function. Usually this takes the form of mild localized edemas and moderate salt retention; sometimes, though quite rarely, of lowered urinary output and mild nitrogen retention. These signs soon disappear upon putting the patient to bed and instituting dietary restrictions, leaving behind the albumin and casts and evidence of focal involvement. These exacerbations with edema and low output, and usually also moderate nitrogen retention, are possibly due to the attendant edema of the kidney, incident to a recent shower of bacterial emboli and the acute inflammatory reaction resulting. This clears up, leaving the focal areas of infiltration with normal kidney parenchyma in between.

The subsequent course of these cases is interesting. In the author's opinion the majority of cases of so-called chronic parenchymatous nephritis come to us through this focal involvement route. Gradually the kidney parenchyma is replaced by scar tissue until we have the irregularly coarse granular kidney classically known as the secondary contracted. As time goes on, and progressively more and more of the kidney cortex is replaced by scar tissue, the periods of anasarca and low output come more frequently and the nitrogen gradually rises as well as the blood-pressure. Finally, we have at the terminal stage the classical clinical picture of chronic parenchymatous nephritis.

The management of these cases must be guided by the amount of functional injury. They develop anemia easily and must not be allowed to suffer from albumin want, since they loose albumin continuously and sometimes in large quantities in the urine. The removal of the focal infection, if accomplished early after the first or at most the second exacerbation, is attended with good results in the majority of cases. Those due to tonsils have the best prognosis. Those where the primary focus is apparently the nasal sinuses do not seem to answer so promptly to surgical treatment of the focus, and in the older cases with frequent exacerbations and even slight evidence of beginning malfunction of the kidney practically nothing is accomplished so far as the kidney is concerned by treating the primary focus.

#### 4. Nephritis Due to Vascular Degeneration.

The fourth group comprises those cases usually designated clinically as chronic interstitial nephritis. There is a diffuse fibrosis of the kidney, as a whole, attended by marked arteriosclerosis and arteriolar thickening. Formerly it was the custom to distinguish

between true interstitial nephritis and chronic "vascular" kidney, but this distinction will not hold either clinically or pathologically. The interesting diffuse changes produced by Newburgh by feeding diets high in protein are of this diffuse interstitial type, and the changes found in the kidney are possibly even here of vascular origin. Ever since the early work of Johnson and Gull and Sutton the importance of which was later emphasized by Jores, the kidney of chronic interstitial nephritis, has been gradually recognized as a part of a general vascular disease. Moscovitz has recently reemphasized the relation of this type of nephritis to generalized arteriosclerosis. The mechanism of the malfunction is in this group most interesting, because, the writer believes, the high blood-pressure in this group is unrelated to the kidney etiologically and is entirely due to the primary arteriosclerosis. It is easy to visualize the pathogenesis of the lesion by examining a series of sections from cases in various stages. We first have the diffuse arteriolar degeneration with thickening of the arteriole walls and lowering of the blood volume delivered to the part in unit time; further, the capacity of the vessels to dilate and contract under different stimuli is lowered. This is a more or less diffuse phenomenon throughout the body. Sometimes the brain is more intensely involved early and we get the clinical manifestations of cerebral arteriosclerosis, or it may be the spinal cord, the pancreas or some other organ is first embarrassed by want of an adequate and variable blood supply by reason of thickened vessels. In many of these cases the kidney escapes completely until apoplexy or some cardiac accident ends the scene. The kidney is, however, frequently involved in the process and partakes of the injury. The point to be kept in mind is that not the kidney but the vascular system is the organ primarily diseased.

During the progression of the arteriosclerosis the blood-pressure has been constantly rising to meet the demands of the tissues for blood. If at this stage we find no kidney malfunction and no urinary evidence of parenchymal injury we are accustomed to use Sir Clifford Albutt's term and say that we are dealing with a case of hyperpiesis. These are the cases in which the kidney has been relatively spared in the general process. If the kidney has not been spared the parenchyma gradually undergoes fibrosis diffusely, the scar tissue becoming hyaline and contracting until we have the very small, finely granular, "primary contracted kidney." At this stage the tubules and glomeruli find themselves diffusely and uniformly killed off until only a number insufficient for function under ordinary conditions are left. But all this time *the blood-pressure has been gradually rising*, due to the arteriosclerosis and not to the kidney injury. *This high blood-pressure allows the few glomeruli to do the work of the many*, and obeying the first law of kidney secretion, the high blood-pressure filters enough fluid through the few glomeruli that are left to keep up the quantity output and chloride elimina-

tion to normal. Anyone who doubts that this is the mechanism has but to observe the behavior of these cases during a cardiac decompensation to be convinced.

The injured glomeruli then are compensated for by the high blood-pressure, keeping the urinary and chloride output up to normal during cardiac efficiency; *but there is nothing to compensate for the injured tubules*. On this account nitrogen retention supervenes and the patient loses his power to concentrate the urine properly because of loss of resorptive power on the part of the tubule. The classical signs of the so-called interstitial nephritis thus can be deduced from the type of injury:

(a) High blood-pressure.

(b) Normal or increased urinary output without salt retention due to the filtration by the high blood-pressure of sufficient fluid through fewer glomeruli than are required under normal conditions.

(c) Urine of low specific gravity and low total solids because the injured tubules are unable to concentrate the urine as well as under normal conditions.

(d) Small trace of albumin and hyaline casts resulting from this type of injury.

(e) Uric acid, urea and creatinine retention because of uncompensated tubular injury.

Many interesting questions arise besides the ones mentioned. It is a question whether the salt hunger manifested by these patients is not really due to salt loss because of inability of the kidney tubule to properly conserve it. In the writer's mind no adequate grounds exist for the restriction on salt often put upon this class of patient.

Clinicians have long ago learned not to try to reduce the blood-pressure in these cases and the importance of the blood-pressure in maintaining the efficiency of the glomerular filters is instantly manifested during myocardial breakdown. Therapeutically the maintenance of the cardiac efficiency and the reduction of the blood nitrogen to the lowest possible level are the major indications. The uremias that supervene require special management not within the scope of this paper. We have a right to expect the best results in those cases detected early. There is some difference of opinion as to just what are the earliest signs of kidney involvement in these cases of hyperpiesis. Probably no one criterion will be discovered to cover all the cases. Newburgh's work suggests that restriction of protein food might be indicated whenever the blood-pressure is abnormally high regardless of laboratory signs of lowered kidney function. The rise in the uric acid level to 3.5 mg. or higher per 100 cc of blood is quite a constant finding in hyperpiesics and probably indicates definitely lowered kidney function. The next sign usually found is an increase in the night urine associated with a delayed meal stimulus and a tendency to fixation of the specific gravity at a low level. This urinary data should be gathered in the

manner suggested by Mosenthal with the patient on the standard diet. The writer prefers to keep the patient on the diet for two days and collect the data during the second twenty-four-hour period.

The clinician now always has the means at hand to collect data from which he can evaluate separately the various functions of the kidney and from them reason back to the lesion. More important than this, the patient's dietary regimen may be made to fit his ability to eliminate, and unnecessary restrictions of protein, water and salt can be avoided.

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### LOWERED VITAL CAPACITY OF THE LUNGS IN A CASE OF PRIMARY HEPATIC TUMOR WITH PULMONARY METASTASES.

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THE following case, which came under observation in the medical ward of the Peter Bent Brigham Hospital, illustrates a condition of considerable rarity and presents several features of clinical as well as pathological interest.

The patient, an unmarried seamstress, aged sixty years, first was seen in the outdoor department of the Peter Bent Brigham Hospital (P. B. B. H., O. D. D., No. 59170) October 2, 1919, where she came complaining of pain and stiffness in both knees of fourteen years' duration, accentuated by motion. She was still able to get about unaided except for the occasional use of a cane. An incidental complaint was that of occasional colicky pains over the upper abdomen, radiating into the back, of ten years' duration, never accompanied by jaundice, occurring most often at night, with rare vomiting. Physical examination at that time showed a blood-pressure of 230 systolic and 124 diastolic, with a coincident mild cardiac hypertrophy, and a soft-blowing systolic murmur not transmitted to the axilla. The knees presented a slight boggy, periarticular swelling, with some pain on manipulation. Lungs, abdomen and the remainder of the examination were reported negative. The urine was normal. She was given potassium iodide and put on a low protein, salt-poor diet. Roentgenograms of both knee-joints were taken which showed definite hypertrophic arthritic changes involving the spine and tuberosities of the tibiae and condyles of the femurs. Throughout that month and the next, she continued under this regimen, with the addition of baking and massage, and reported some improvement in her knees. Only on one occasion did she complain

of a slight cough, which promptly subsided. Two and a half months later she had developed tiredness, palpitation and a slight dyspnea on exertion, which apparently were taken as manifestations of her cardiovascular condition, and nitroglycerin, .06 mg., t. i d., was prescribed, with subsequent improvement, though she continued to fatigue easily.

Thereafter her course was uneventful, until August 25, 1920, when she returned with her former complaints, and in addition mentioned that she had been expectorating small amounts of blood-streaked sputum occasionally at night. Flat and stereoscopic roentgenograms of the chest (Fig. 1) were taken with the following report: "The chest is symmetrical with a normal diaphragm, which

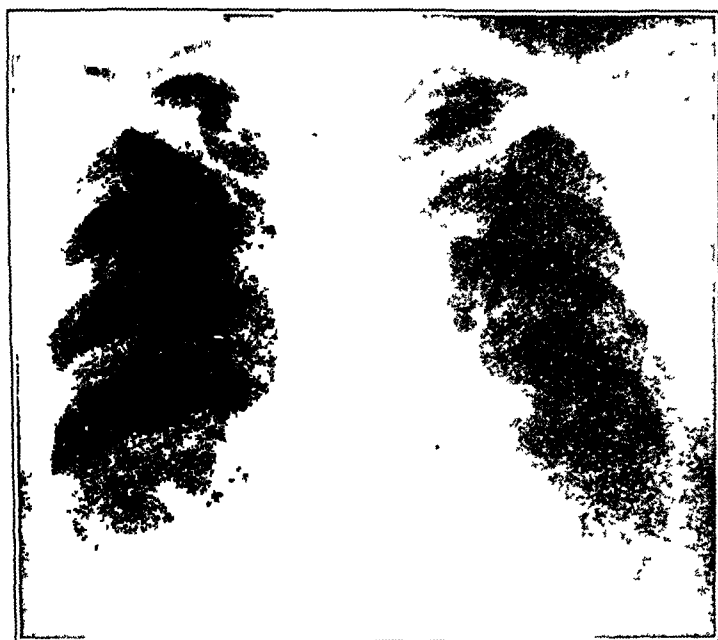


FIG. 1.—Roentgenogram of the chest, taken August 27, showing marked increased infiltration about the roots of both lungs, and metastases into the lung fields themselves, the latter being more numerous in the lower lobes, though the original plates show a definite upper lobe metastasis as well.

moves freely during respiration. The trachea is in the midline. There is a marked increase in the density of the root shadows, especially on the right side, which definitely shows glandular enlargement. There is a bilateral 'spotty' consolidation throughout both lungs, most marked in the lower lobes. This consolidation has every appearance of being metastatic malignancy, and not tuberculosis." Barium studies of the gastro-intestinal tract, instituted thereafter in search of a primary source, were entirely negative, and as the patient was commencing to have more copious hemoptyses, she was sent into the hospital on September 16.

An additional and more complete history relative to her pulmonary condition gave a present illness of one month's duration, the



chief symptoms of which were an increasing sense of "tightness" in the chest, some "wheezing" on breathing, progressing dyspnea, occasional slight hemoptyses and insomnia. With these were associated increasing weakness and a loss in weight of about twenty pounds.

*Family History.* Her father and both paternal grandparents had died in middle age of tuberculosis. Her mother died at forty-seven of "shock."

*Marital History.* The patient was single and of abstemious habits. She had always lived in Boston or vicinity.

*Past History.* Measles at six, "intermittent fever" at sixteen, and malaria at forty-six were her only acute infections. Following vague pelvic symptoms she was operated upon about ten years ago and double oöphorectomy and hysterectomy were performed, and she was told that gall-stones were found in the gall-bladder, but that her condition prevented further investigation. Otherwise, there was nothing of importance in her history, except for a long-standing nocturia and the previously mentioned arthritis in the knees.

*Physical Examination.* Showed a well-developed and rather undernourished adult female of sixty-one years, lying comfortably in bed without pain or dyspnea and mentally coöperative. Skull, scalp, hair, face and skin were negative. Eyes were normal except for a slight irregularity of the pupils and a temporal hemianopsia, probably explained by a partially formed cataract in the right eye. Ophthalmoscopic examination was negative. Ears, nose, mouth and lips were normal. Teeth showed a few of the upper incisors remaining; the lowers were missing. Tongue, tonsils, pharynx and neck were normal. A persistent huskiness was noted in the patient's voice, which she said had always been present. The thorax was symmetrical and expanded equally on both sides; no abnormalities were noted. The heart showed the left border of dulness 10 cm. from the midsternal line and the right border of dulness at the right sternal margin; the supracardiac dulness was not increased. Sounds were regular and of good quality, and there was a soft-blowing systolic murmur best heard at the apex. Pulmonary and aortic second sounds were somewhat accentuated. The vessels were relatively normal. Blood-pressure: systolic, 180; diastolic 90. Lungs, tactile and vocal fremitus were well transmitted and breath sounds were bronchovesicular throughout both lungs. Percussion showed questionable small areas of dulness posteriorly, most marked in the region of the hila. Fine crepitant rales were heard throughout the left lung and there were a few fine moist rales at the right base behind and over the right lower chest anteriorly. The right border of the diaphragm was higher than the left and expansion of the bases was only fair. The abdomen was reported negative, except for the epigastrium and right hypo-

chondrium, over which there was an increased resistance to palpation, with the sensation of an underlying mass, the character of which, however, could not be determined on account of the rigidity of the abdominal musculature. Since the liver dulness extended from the sixth rib above to three finger-breadths below the costal margin it was felt that there was an enlargement of that organ. Gall-bladder, spleen and kidneys were not palpable. There was no peripheral adenopathy and the bones and extremities were not remarkable. Vaginal and rectal examinations revealed no pathology, except that the fundus uteri could not be felt.

**Clinical Course of the Disease.** Subsequent examinations by various members of the house and visiting staff bore out the entrance physical findings. However, as palpation of the mass in the right upper quadrant was so unsatisfactory and enlargement of the right kidney could not be ruled out, pyelograms and cystoscopic studies were suggested for this purpose. The latter showed no evidence of genito-urinary lesions and the former demonstrated both kidneys in normal position with normal pelves and calices. Incidentally multiple gall-stone shadows were seen overlying the right kidney shadow and there was a distinct sacralization of the fifth lumbar vertebra.

Subjectively, for the succeeding three weeks, the patient's condition changed very little, except for a gradually increasing weakness. She continued to expectorate varying amounts of a more or less blood-streaked sputum, and although during the first ten days she lost about six pounds in weight, in the following week she regained one and one-half pounds. The number and location of rales heard over both chests varied considerably from one examination to the next, but breath sounds over the left lung had become distinctly cog-wheel in character.

A note by Dr. Henry A. Christian on October 7 follows: "The epigastrium down to a point two fingers above the navel is elevated by a mass which moves distinctly with respiration. It has a fairly distinct lower rounded border. It can be traced across the abdomen from the left costal margin in the anterior axillary line to the right flank at the level of the anterior-superior spine of the ileum. The mass is firm. The surface is smooth. It seems to be an enlarged liver. The gall-bladder cannot be felt."

Further roentgen-ray examination of the chest at this time (Fig. 2) showed the condition there to be considerably more advanced than before, with increased density of the glands about the left hilum.

From this point the patient's condition became progressively worse. On October 18 she complained of loss of appetite, which to that point had been sustained, and of a sensation of "choking up" in the chest, with expectoration of larger quantities of blood. There were now numerous crepitant rales throughout both lungs, moist

rales at the bases and friction rubs in either axilla. The liver enlargement remained as noted above. By October 27 insomnia became a prominent symptom, chest pain and respiratory difficulty were much more marked and the voice became increasingly husky, for which laryngoscopic examination revealed no cause. Repeated vaginal and rectal examinations had continued negative and other signs were as above. Thereafter the various factors increased in intensity, and the patient died, apparently of respiratory failure, at 1.30 A.M., November 1, her forty-seventh day in the hospital.

*Temperature.* The morning temperature varied from  $96.8^{\circ}$  to  $99^{\circ}$ , averaging  $98^{\circ}$ , while the evening temperature varied from  $98^{\circ}$  to  $100.2^{\circ}$  averaging slightly over  $99^{\circ}$ .



FIG. 2.—Taken October 7, showing the metastases much more numerous, and the root infiltration more extensive than on the first plate.

*Pulse* averaged 90 until the last ten days in the hospital, after which it underwent a steady increase, reaching 130 on the four days preceding exodus.

*Respiration* remained at 20 per minute until one week preceding death, at which point it suddenly rose to 35 and remained between 30 and 40 until the end.

*Weight* fell steadily but for one transient rise, from 63.6 kg. at entrance to 58.3 kg. one week before exit.

*Blood-pressure.* Weekly determinations showed systolic readings varying from 180 to 200 during the first two weeks and from 158 to 174 in the last five weeks, and diastolic from 90 to 110 during the first period and from 70 to 90 in the latter.

*Vital Capacity of the Lungs.* As compared with a normal of 3120 cc for a person of the patient's sex, age, height and weight her vital capacity was 1200 cc (41.5 per cent) five days after entry, rose to 1300 cc at the end of three weeks and fell to 800 cc ten days before death. From that time on her bodily discomfort was too great to permit of further trials.

*Clinical Pathology.* (a) Blood Wassermann negative.

(b) Phenolsulphonephthalein output normal.

(c) Gastric analysis showed a normal acidity curve. Benzidine test for occult blood was negative in all specimens and microscopical examination revealed no abnormalities.

(d) Sputum examinations, made at least bi-weekly, showed almost routinely a frothy, watery material, streaked with fresh blood and a stringy mucopurulent substance. Careful search for tubercle bacilli or bits of tumor tissue were consistently without positive results; organisms were present in moderate numbers, the predominating type being Gram-positive cocci, arranged in pairs and chains of varying lengths.

(e) Stool examination was constantly negative.

(f) Blood: Hgb. (Tallquist) varied from 80 per cent on entry to 65 per cent two days before exodus. White blood cells varied from 6000 on first count to 9200 on the evening before death, with a tendency toward a gradual slow rise. Red blood cells remained, within limit of error, at 4,300,000 during the entire course. Smear done on entry showed a normal differential count, and no abnormalities in shape, size or color of red blood cells.

(g) Urine showed no fixation of specific gravity and was negative for albumin, sugar and important sedimentary findings, except after cystoscopy, when a large trace of albumin appeared and the sediment showed a large number of red blood cells.

The antemortem diagnosis, therefore, on the basis of the above was metastatic malignancy of the liver and lungs; primary source undiscovered.

**Pathology.** Autopsy performed thirteen hours post mortem by Dr. Victor C. Jacobson shows the following findings:

General external examination is essentially negative except for a rather pendulous abdomen, marked by many lineæ atrophicæ.

*Peritoneal cavity* shows no free fluid. The omentum is firmly adherent to the peritoneum along the line of the abdominal scar. The liver is very prominent, being pushed downward and forward, its lower border 15.5 cm. below the xiphoid and 7 cm. below the right costal margin. The spleen is covered by the left lower ribs. The appendix, uterus, tubes, and ovaries are not present, only a short cervical stump remaining. The diaphragm is on a level with the lower border of the third rib on the right and with the fourth rib on the left. The mesenteric lymph nodes are very small and lie embedded in much mesenteric fat.

*Pleural cavities* are practically obliterated by the adhesion of the lungs to the parietal pleuræ, which is rough and nodular from the presence of innumerable, irregularly rounded projections of tumor, varying in size from that of a pinhead to that of the largest on the diaphragmatic pleura, which is about 2 x 3 x 3 cm. These nodules are dark red, streaked with white, very firm and usually surrounded by radiating, dilated veins. In the right cavity 250 cc and in the left 150 cc of a blood-tinged fluid is found.

*Mediastinum.* The under surface of the sternum is studded with tumor nodules 0.2 to 2 cm. in size. The mediastinal fat is of normal amount and shows no tumor growths. The organs are in normal position.

*Pericardial cavity* is normal.

*Heart* shows nothing of importance.



Fig. 3—Photograph of the liver tumor (much reduced) showing extension into a hepatic vein

*Lungs.* The right and left lungs weigh 710 and 705 grams respectively, are similar in appearance and of about half their normal size. The pleural surfaces are rough and nodular, due to the presence of a large number of rather hard, pale white, circumscribed growths, varying in size from 1 mm. to 2 cm. and projecting about 3 mm. above the surface. These are found all over the pleura, and while the lymphatics are fairly prominent, these tumors do not seem to be intimately connected with them. About many are radiating, dilated venules. Between these nodules the tissue is rather elastic, slightly crepitant and grayish red. The glands at the hila and also at the bifurcation of the trachea are 1 to 2 cm. in size, many are very firm, and on section are opaque white,

streaked with red. A lateral incision in each lung (Fig. 4) shows a widespread distribution of the tumor nodules, similar to those on the pleural surfaces. They vary in size as in the pleura and are diffusely distributed throughout the lung lobules. Many are colored with carbon pigment or surrounded by a narrow black ring of anthracosis. The tumor growths appear to arise chiefly in the small arterioles and the picture is much different from that of metastasis by way of the lymph stream. The tissue between the tumors varies in color from gray to deep red and in consistence from elastic to firm and méaty. Thrombi occlude many of the



FIG. 4.—Photograph of section through right lung, showing metastatic nodules.

arterioles, but the larger vessels are empty. In some of the bronchioles, dark red blood clots are found in which are small particles of opaque-white tissue, suggesting tumor. The trachea shows moderate injection of the mucosa.

*Spleen* is about twice its normal size, dark red and firm.

*Gastro-intestinal tract* is normal.

*Pancreas* is dark red and rather soft in consistence. The pancreatic duct is dilated, but there is no bile-staining, stone or plug of any kind. The lobules are well marked but hemorrhage has occurred between practically all, with some staining of the lobules.

No fat necroses are seen and the pancreatico-duodenal artery is normal as far as can be dissected.

*Liver* is much enlarged (weight 2360 grams), particularly in its right lobe, which on its lateral and posterior surfaces is firmly adherent to the diaphragm. This is due to the presence of a mass occupying about half of the right lobe and extending outward so that a protuberance with pearly white borders and a dark red, depressed central portion projects about 1 cm. above the surface over an area about 12 cm. in diameter, forming a growth shaped more or less like a group of rosettes. The diaphragm appears to be invaded and streaks of grayish-white, very probably tumor tissue, run from the liver tumor to the large nodules on the pleural surface of the diaphragm. Sections through the liver (Fig. 3) at various angles show that the gross tumor is limited to the large mass in the right lobe, the remainder of the organ having only a moderate "nutmeg" appearance. This tumor is fairly well circumscribed and its greatest diameter is 15 cm. It is of almost cartilaginous hardness and has no definite capsule, though clearly rounded edges. There is a distortion of the liver lobules adjoining it, probably due to pressure. The tumor is not bile-stained and there is no gross evidence of bile stasis. Dissection shows that the larger bile ducts leading to the tumor abruptly stop when the tumor is reached. Small branches of the hepatic vein in the vicinity of the tumor contain thrombi and a few of them flecks of grayish-white, quite firm tissue, possibly tumor. The ducts and vessels of the rest of the liver show no lesion.

*Gall-bladder* is but 0.5 cm. from the tumor, but its mucosa moves freely over the subjacent tissues and appears normal. Eight black, faceted calculi, 1.5 cm. in size, lie free in the gall-bladder. The cystic, hepatic and common ducts in the porta hepatis show no stones or tumor. Two lymph glands at the junction of the cystic and hepatic ducts are enlarged and firm, but are pale and do not appear to contain tumor.

*Kidneys* show nothing of importance except two small cysts in the substance of the cortex of the right kidney.

*Genitalia.* Only the stump of the cervix remains and a red, pedunculated polyp, 2 x 0.5 cm., is attached to the midportion of the cervical mucosa, bathed in a reddish, mucoid secretion.

*Aorta* shows moderate intimal thickening of the arch; the vena cava inferior contains no thrombi.

*Microscopic Examination. Heart.* A fairly large area of a section through the left ventricle shows degeneration of the muscle fibers and replacement by young fibroblasts and congested capillaries.

*Lung.* There are two sections showing processes that are alike. These are for the most part filled with tumor that appears as nests of epithelial cells surrounded by a connective stroma and as cavities lined by epithelial cells of several layers of thickness. Most of

these cavities show a tendency in their walls to grow in toward the center, giving the appearance of an adenocarcinoma. Tumor cells are seen to plug many of the veins. Mitotic figures are numerous. The remaining portions of the sections show congestion of the alveolar capillaries and many small areas of organizing pneumonia. Large numbers of desquamated epithelial cells and a few polymorphonuclear leukocytes are seen in many alveoli. A few of these contain plugs of fibrin and invading fibroblasts. A section of the trachea and attached lymph node shows no tumor.

*Lymph node* (bronchial) is surrounded by a thick capsule and contains abundant carbon pigment. The central portion shows an extensive invasion of tumor, the cells and their arrangement being similar to the tumor elsewhere.

*Diaphragm.* The section consists of striated muscle and tumor. The muscle fibers in the region of the tumor are replaced by hyalinized fibrous tissue. Sections of dense fibrous tissue that have become hyalinized in places contain many irregular cavities filled with tumor cells.

*Spleen.* That of chronic passive congestion.

*Liver.* There are four sections showing processes more or less alike. The more conspicuous of these are the numerous foci of tumor cells. These appear as elongated and cuboidal epithelial cells, basic stained, having large, finely granular nuclei and a narrow rim of clear cytoplasm. While some of the cells are loosely scattered the tendency is for them to form columns, supported by delicate fibrous strands. In places there are wide trabeculae of connective tissue. In the portal areas there is a proliferation of fibrous tissue and bile ducts. Many of the latter have an epithelial lining several layers thick, partially occluding the lumen, while in others the epithelial cells have ruptured the basement membrane and invaded the surrounding connective tissue stroma. The tumor cells in general are in every respect similar to those of the bile capillaries, a feature which indicates the origin of the tumor. There is pressure atrophy of many of the liver cells as a result of the tumor invasion and marked congestion of the sinuses. Many show necrosis, particularly about the central areas, where many polymorphonuclear leukocytes are seen in the sinuses. Other liver cells show tremendous fatty infiltration. Some of the smaller branches of the hepatic veins contain tumor.

*Kidney.* There is but one section, that showing the picture of a chronic passive congestion with thickening of the capsule. There is connective tissue increase and slight thickening of the glomerular capsule with atrophy of the tufts beneath it. In this region two or three groups of tumor cells are seen, both as irregular tubules and as small nests in the connective tissue. A small hemorrhagic infarct is present in the cortex of the kidney.

*Pancreas* shows acute hemorrhagic necrosis, probably agonal.



**Anatomical Diagnosis.** Massive adenocarcinoma of the liver (primary), with metastases to the lung, pleuræ, mediastinal lymph nodes and kidney. Pleural effusion (bilateral). Acute hemorrhagic pancreatic necrosis. Chronic fibrous myocarditis. Cholelithiasis. Cervical polyp. Absence of uterus, tubes, ovaries and appendix (operative).

**Discussion.** The *raison d'être* for the report of this case lies not so much in the underlying pathology which it presents as in the interesting clinical features which make it, I believe, unique among cases of this variety.

Primary carcinoma of the liver is relatively a rare tumor, its average incidence in the autopsy rolls of ten of the world's largest clinics being about one in every thousand autopsies. Eggel<sup>1</sup> reviewed 163 cases reported up to 1901 and some 150 have been added since by various writers, especially Fischer,<sup>2</sup> Acland and Dudgeon,<sup>3</sup> Pepere,<sup>4</sup> Dibbelt,<sup>5</sup> Oertel,<sup>6</sup> Colwell,<sup>7</sup> Polak-Daniels,<sup>8</sup> Wegelin,<sup>9</sup> Grawitz,<sup>10</sup> Gravina,<sup>11</sup> Herxheimer,<sup>12</sup> Hawes,<sup>13</sup> Cade,<sup>14</sup> Loehlein,<sup>15</sup> Wheeler,<sup>16</sup> Karsner,<sup>17</sup> Goldzieher and v. Bokay,<sup>18</sup> Amlinger,<sup>19</sup> Winternitz,<sup>20</sup> Okazski,<sup>21</sup> Muir<sup>22</sup> and Milne.<sup>23</sup>

Generally speaking, from the standpoint of morbid anatomy, primary carcinoma of the liver arises from a proliferation of the liver cells or from the cuboidal or columnar epithelium of the intrahepatic bile ducts. They are divided broadly into three groups: (a) Nodular, resembling multiple secondary nodules, except that no primary focus can be found, and constituting, in Eggel's careful review, 64.6 per cent of his cases; (b) massive, consisting of a large white or yellowish "mother-tumor," occurring

<sup>1</sup> Beitr. z. path. Anat. u. Physiol., Jena, 1901, 30, 506.

<sup>2</sup> Virchow's Arch. f. path. Anat., 1903, 174, 545-563.

<sup>3</sup> Lancet, 1902, 2, 1310.

<sup>4</sup> I Tumori maligni Primarii del Fegato, 1902, p. 171.

<sup>5</sup> Ueber hyperplas., adenom. u. prim. Krebs der Leber, Greifswald, 1903, F. W. Kunike, p. 61.

<sup>6</sup> Virchow's Arch. f. path. Anat., 1905, 158, 499-515.

<sup>7</sup> Arch. Middlesex Hosp., London, 1905, 5, 123-141.

<sup>8</sup> Ztschr. f. Krebsforsch., Berlin, 1905, vol. 28.

<sup>9</sup> Virchow's Arch. f. path. Anat., 1905, 179, 95-153.

<sup>10</sup> Deutsche. med. Wchnschr., 1905, 31, 284.

<sup>11</sup> Gazz. internaz. d. Med., 1905, 8, 63-65.

<sup>12</sup> Centralbl. f. allg. Path. u. path. Anat., Jena, 1906, 17, 724.

<sup>13</sup> St. Bartholomew's Hosp. Rep., 1905, London, 1906, 41, 161.

<sup>14</sup> Lyon méd., 1908, 110, 785-789.

<sup>15</sup> Beiträg. z. path. Anat., etc., Jena, 1907, 42, 531-553.

<sup>16</sup> Guy's Hosp. Rep., London, 1909, 68, 225-244.

<sup>17</sup> Arch. d. Med., 1911, 8, 238-261.

<sup>18</sup> Virchows Arch. f. path. Anat., 1911, 203, 75-131.

<sup>19</sup> Primary Carcinoma of Liver with Metastasis to the Lungs, Bonn, 1911, J.

Trapp.

<sup>20</sup> Johns Hopkins Hosp. Rep., 1916, 17, 143.

<sup>21</sup> Sei-I-Kwai Med. Jour., Tokyo, 1915, No. 1, vol. 34.

<sup>22</sup> Jour. Path. and Bacteriol., 1908, p. 287; 1911, p. 389.

<sup>23</sup> Ibid., 1909, p. 318.

usually in the right lobe and forming 23 per cent of Eggel's cases; and (c) diffuse, wherein the growth extends widely throughout the organ, perhaps without gross increase in its size, histogenetically practically always spheroidal-cell in type, and numerically composing 12 per cent of the cases. Sauborin,<sup>24</sup> Hanot and Gilbert<sup>25</sup> and others have attempted to add a fourth group, "cancer avec cirrhose," but since cirrhosis is so frequent an occurrence in all groups (various observers reporting it in one-quarter to one-half of all cases), this close interrelation to the original three seems to make this addition superfluous.

Eggel classes but 27 of the 117 cases which are described microscopically as of the massive type, and of these but 3 (or less than 3 per cent) are considered to be of bile-duct origin. Other observers, among whom are Herxheimer,<sup>12</sup> and B. Fischer,<sup>2</sup> have contended that 50 per cent of the cases classed by this author as of liver-cell origin are in reality bile-duct cancers; but their arguments are unconvincing, hence for the present at least we will abide by the opinion of the original observer.

Unfortunately, however, a grouping of the hepatic carcinomata on this basis is not as simple as these headings might lead us to believe, for there is a pronounced overlapping throughout, and in addition there are further subheads separating "solid" and "adenomatous" tumors as well as those of liver-cell and bile-duct origin. Hence we shall not concern ourselves further with the vagaries of classification but rather proceed to a discussion of the case at hand.

Etiologically we are on no more familiar ground than in malignancy elsewhere, though the relative frequency of an alcoholic history, as well as the common coincident hepatic cirrhosis, favors the view that, in a certain proportion at least, "we have a vicarious hypertrophy, which, from some unknown cause, proceeds past its goal and by atypical growth leads to the formation of a tumor" (Orth,<sup>26</sup> Schmeiden;<sup>27</sup>) or, in the words of Rolleston,<sup>28</sup> "There is an acquired habit of proliferation of the liver cells which, starting as a compensatory hyperplasia and thus giving rise to multiple adenomata in cirrhosis, eventually becomes so excessive as to constitute carcinoma." It is interesting that whereas gall-stones are so common a finding in carcinoma of the extrahepatic bile ducts and gall-bladder (in 80 to 90 per cent of cases according to most statistics), in the type under discussion they seem to be but occasional incidental occurrences, found in none of 41 cases and in but 5 of 25 cases in the series reported from two large London hospitals. There are, of course, the usual references to trauma and heredity,

<sup>24</sup> Essai sur l'adenome du foie, Th. doct., Paris, 1881.

<sup>25</sup> Études sur les maladies du foie, Paris, 1888, p. 30.

<sup>26</sup> Path. Anat., 1887, s. 955.

<sup>27</sup> Virchow's Arch., 1900, 154, s. 290.

<sup>28</sup> Diseases of the Liver, Gall-bladder and Bile Ducts, Macmillan, 1914.

and, under the latter, Hedinger<sup>29</sup> cites an unusual pair of cases in which two sisters, aged seventy-one and seventy-seven years, came to autopsy in his clinic within the same week, each showing a definite primary carcinoma of the liver. However, aside from this single unique observation, the hereditary factor is more conspicuous by its absence than otherwise.

*Incidence.* (a) *Age:* Although Eggel's figures and those of the majority of writers on this subject show that a large majority of cases fall within the so-called "tropic of cancer," Castle<sup>30</sup> has reported 42 cases, all apparently authentic, and to these Griffith<sup>31</sup> has added 15 more, occurring under sixteen years. The relatively high incidence in the first year (28 per cent) points toward a possible congenital factor in many of these juvenile tumors.

(b) *Sex:* Contrary to the finding in secondary carcinoma of the liver, but in keeping with cirrhosis itself, the male incidence definitely predominates (63 per cent in Eggel's series).

*Location.* Of the above-mentioned 27 cases of carcinoma of the massive type, 18 were in the right lobe alone, 6 in the left alone and 3 showed a generalized infiltration.

*Clinical.* Symptomatically there is an unusual uniformity in the list of complaints recorded, which consist in the main of general weakness, a sense of epigastric fulness proceeding later to epigastric or right upper quadrant pain, occasional dyspnea and often diarrhea. Physical examination reveals (a) jaundice, usually relatively mild, in about 60 per cent of the cases reported; (b) ascites, frequently hemorrhagic, in about 58 per cent; (c) edema, most often of the lower extremities, in 40 per cent; (d) splenic enlargement in 32 per cent; and (e) fever, practically always of a very moderate grade, 14 per cent; with (f) tenderness on pressure over the hepatic area in a large majority of cases. The postmortem evidence has rather frequently shown pulmonary metastases, contrary to the teachings of most text-books on the subject, but in no previous case which I have found has the new growth there been of sufficient extent or importance to have given abnormal findings on the physical examination of the chest during life.

With the rather sparse signs found over the chest in the present case, our first evidence of the real extent of the pulmonary process came from the observation of the pulmonary "vital capacity" of the patient or the volume in cubic centimeters of "the greatest possible expiration after the deepest possible inspiration," as recorded on the ordinary water spirometer. It is a measurement, in short, of the depth to which the respiration can be increased. Peabody<sup>32</sup> has recently given an admirable discussion of this subject with a thorough review of the literature on it. Normal standards

<sup>29</sup> Centrallbl. f. allg. path. Anat., 1915, 27, 385.

<sup>30</sup> Surg., Gynec. and Obst., 1914, 18, 477.

<sup>31</sup> Am. Jour. Med. Sc., 1918, 79, 155.

<sup>32</sup> Oxford Medicine, 1910, 1, 599-609.

have been established for both sexes with respect to the individual surface area, as determined by the height and weight table of Du Bois.<sup>33</sup> Results in children and in individuals over forty have not been published, but from personal observation in a considerable number of the latter there seems to be a decrease normally to 75 to 80 per cent of the normal standard for younger adults, as the tissue elasticity grows less. However, as the lowering of the vital capacity in the case under discussion was about 41 per cent of normal on entrance, it is seen that the change is pronounced enough to be a distinct guide in diagnosing the scope of the lung pathology, and this was further borne out by the continued fall as the process advanced clinically and roentgenologically.

**Summary:** 1. The case under discussion is one of primary carcinoma of the right lobe of the liver, originating from the epithelium of the intrahepatic bile ducts.

2. Metastases are demonstrated in the liver substance, in glands at the lung hila, in the kidney and seeded throughout the parenchyma, pleuræ and bloodvessels of both lungs. Numerous thrombi are found in the hepatic veins.

3. Many of the classical features of tumors of this type, *i. e.*, the right upper abdominal quadrant pain, jaundice, ascites and edema, are lacking. The pulmonary symptoms, thoracic pain, dyspnea and hemoptysis, led to the patient's entrance into the hospital and dominated the picture throughout, producing the most interesting phase of the case, the marked reduction in vital capacity as compared with the relative insignificance of the pulmonary signs. The change in vital capacity furnished the first real evidence of the extent of progress of the intrathoracic process, which was later demonstrated in the autopsy room.

In conclusion, the writer wishes to acknowledge his obligation to Dr. Victor C. Jacobson for his kind assistance in the pathological study of the case.

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## THE EARLY MANIFESTATIONS AND RATIONAL TREATMENT OF TABES DORSALIS.

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OUR conception of tabes dorsalis, the most common of the chronic diseases of the spinal cord, has undergone many changes during recent years. That it was in some way related to syphilis was early recognized by Fournier and his contemporaries, but the fact that the common manifestations of syphilis had usually been in abeyance

<sup>33</sup> Arch. d. méd., 1916, 17, 855.

for many years when the symptoms of tabes made their appearance, led to the belief that it was a sequel rather than a manifestation of an active syphilitic process. It was accordingly considered as a parasymphilitic affair until the modern methods of spinal fluid examination conclusively established its syphilitic nature. It is now believed that infection of the nervous system takes place at the time of maximal spirochetal mobilization in from 25 to 35 per cent of cases, that is during the period of secondary manifestations<sup>1</sup>. It is interesting to speculate why so many years elapse after infection before symptoms appear. Warthin has demonstrated that spirochetes may, for a time at least, lie between the cells of the heart muscle without producing any change in the adjacent cells. It is possible that the same thing obtains in nervous tissue. We know that the changes produced by syphilis are brought about very slowly. Years elapse between the beginning of the perivascular infiltration about the vasa vasora in the adventitia of the aorta and the appearance of aneurysmal symptoms. The same must be true when the nervous system is attacked. In some cases trauma seems to precipitate the symptoms; in others exposure, overwork, excesses, etc., appeared to be responsible. It has been suggested<sup>2</sup> that the initial implantation of spirochetes in nervous tissues does not constitute an infection, as we usually understand it, but produces rather a sensitization or a condition of "hyperallergie." Later, when, as the result of some of the causes already enumerated, there is a fresh mobilization of organisms or their toxins, flooding of the nervous system results, with activation of the previously established foci. Thus it is that a reaction in hypersensitive tissue, even though there be relatively few spirochetes present, may be of serious nature and lead to grave tissue destruction. Before discussing the symptomatology and physical signs it may be well to briefly consider the present conception of the pathology. It is now believed that the degeneration in the columns of Goll and Burdock is not primary but secondary to change in the posterior roots and ganglia. *The process probably begins as a slowly progressive meningitis, often minute in extent, about the posterior roots proximal to the ganglia.* The small vessels of the pia arachnoid show a perivascular plasma and round-cell infiltration. This inflammatory process, possibly by pressure, results in a degeneration of the ganglia and of the centripetal roots, which is followed by an ascending degeneration in the posterior columns. It is at once apparent that *recognition of the symptoms and signs that precede the stage of degeneration is of paramount importance if our therapy is to avail.*

A basilar meningitis is frequently present and implication of the cranial nerves often follows, especially the third, fourth and sixth; in fact, this may be the first evidence of involvement of the nervous system. The most dreaded of all manifestations, optic atrophy, is now thought to be secondary to meningitis. Degeneration of the

peripheral sensory neurons has long been recognized, but the sequence of its occurrence has not been definitely determined. Both Ehrman and Levaditi<sup>3</sup> have shown that the *Spirocheta pallida* may pass from the primary lesion up the peripheral nerves; they have discovered the organism not only in the lymph spaces of the perineurium, but actually between the nerve fibers.

Orr and Rows<sup>3</sup> have shown experimentally that toxins introduced into the sheaths of the peripheral nerves will produce "tabetic lesions" in the cord; they believe tabes results from lymphogenous infection. From the extensive and varying pathology it is obvious that the symptomatology must be exceedingly diverse and often confusing. Curious complexes arise, due to the fact that certain sensory neurons are in a state of acute irritability causing pain, while others, more or less completely degenerated, cause varying degrees of anesthesia and paresthesia. The difficulty in walking, for instance, so apparently a motor difficulty, is not due to motor-tract involvement but the degeneration of the sensory neurons with resulting loss of the sense of position. Because of the great variety of symptoms we see tabetics seeking relief not alone from their family doctor but from the specialist in "rheumatism," the orthopedist, the gynecologist and the eye, ear, throat and nose specialist. We see them swallowing stomach tubes, duodenal tubes and barium meals; using vibrators and electric batteries; being robbed of their prostates, and periodically having their abdomens explored. One is impressed in taking the history of these unfortunates not only with the long period of time that intervenes between the primary infection and the development of symptoms but by the number of years that often elapse after seeking relief before the nature of the trouble is recognized. In order to illustrate this varied symptomatology I have reviewed the histories of 60 cases comprising hospital, referred and private patients seen during the past few years. Thirty per cent were females and 70 per cent males. The average age of the women was forty years and of the men forty-five years. A history of syphilis was present in 45 per cent of the men but in only 16 per cent of the women. In 4 cases the infection appeared to have been prenatal; in 6 others this was suggested.

*Pain is by far the most common symptom complained of.* The common term "lightning pains" well describes their sudden onset, stabbing nature and rapid abatement. They were present in over 60 per cent of this series. The pains, however, are not always so intense and characteristic, and sciatica may be closely simulated. Numbness and tingling in the extremities, most commonly in the feet, also "drawing" sensations in the feet, are common symptoms and may precede the pains by a considerable period, but because of their unobtrusive character are often disregarded by the patient. While pain is the chief symptom, careful questioning will frequently reveal that other symptoms, perhaps more characteristic of the

condition than the pain, have existed for some time previously. It is, for this reason, important that a complete history be obtained, whenever patients complain of vague pains in various parts of the body, as the fitting together of isolated and in themselves insignificant data will oftentimes enable one to make a diagnosis that the blood and spinal fluid examinations will substantiate.

CASE I.—When J. H. was thirty-nine years old he began to notice that he would have *sharp, fleeting pains just above his heels in the evening*; if at a meeting he would frequently have to retire, as walking about caused the pains to disappear. There was also a “drawing sensation,” as though his feet were in a vise. These pains were suggestive, but their significance was increased many fold by the fact that for several years he had noticed that *he could go for many hours without any inclination to pass his urine*, and that when he did void he passed a large amount. These symptoms slowly increased and his hearing began to fail. About *five years later incontinency* began and the urine became foul. At this time, ten years after the first symptoms and twenty-five years after his chancre had been cauterized, he was referred to a surgeon for prostatectomy. Fortunately the surgeon happened to be the late Dr. O. C. Smith, who recognized a cord lesion and referred him to me for treatment.

Bladder symptoms are mentioned as occurring early in 43 per cent of this series. This percentage I think would have been increased if more care had been taken in investigating it. *Unconscious distention of the bladder is often the earliest symptom*, frequently preceding incontinency by many years. It does not seem that this symptom has received the attention that it merits. The loss of bladder sensibility to distention develops so insidiously that the patient is usually unconscious of it until specific inquiry directs his attention to it. If he has noted it he may likely consider it a convenience rather than an omen of serious import. He may state that he can “go all day” without voiding, and will then pass a large amount. Some delay in initiating the act and in its completion may be present. The diminution of bladder sensibility may precede the development of lightning pains by several years. The characteristic cystoscopic appearance of the bladder wall will be referred to later.

So gradual may be the loss of conductivity of the centripetal neurons that originate in the skin, muscles and joints, and keep us advised as to the position of our extremities, that *unsteadiness in performing accustomed movements may first be noticed by others*. Thus a man who considered himself well was told by friends that he walked as though intoxicated. It is not uncommon for patients to note unsteadiness in going up and down stairs as the first symptom, though they will often acknowledge that their feet had felt numb for

a time previously. The first symptom one woman noticed was that she bumped against the corners of the table when walking about her living room and found it necessary to steady herself; this was several years before the lightning pains began. Another woman first noticed difficulty in threading her needle, apparently due to lack of coördination or diminished tactile sense rather than to poor vision. A married woman, aged forty years, first noticed a numb, dead feeling in the outer aspect of the lower third of the left thigh. Later the same sensation extended over the sides of the chest and the right shoulder. It was not until several years later that the development of severe leg pains caused her to seek relief, at which time the signs of tabes were definite. *Sometimes the symptoms are typical of what we term neurasthenia.*

CASE II.—A man, aged thirty-six years, complained of a nervous feeling in his stomach and "gas," and nervousness in his back and insomnia. He was too nervous to work. The stomach symptoms were by far the worst, and a specialist washed his stomach on eighty consecutive days. When I saw him several months later he was an advanced taboparetic.

The marked dissimilarity in symptomatology is well shown by two cases that were in the women's ward on Dr. Cochran's service at the hospital at the same time a year ago. They also illustrate that the physical signs are not always the same.

CASE III.—H. H., a woman, aged thirty-nine years, had been in her usual health, save for some blurring of vision occasionally and a slight cough, until four days before admission to the hospital. At this time, while bending over her work, she was seized with a feeling of numbness and a sensation of "pins and needles" around the toes. The legs were very weak and she had difficulty in walking upstairs. The following day the same tingling developed in the fingers of both hands and spread up the arms. The day after admittance to the hospital she could not stand alone. The *pupils were unequal, dilated and immobile, the deep reflexes were absent*, the Wassermann was positive in the blood and spinal fluid and the colloidal-gold test gave a paretic curve.

An entirely different picture was present in the next case.

CASE IV.—A married woman, aged twenty-six years, complained of *palpitation and dyspnea*. Eight weeks before she had a curettage following a criminal abortion; one week later she began to have *tachycardia* and became short of breath. A little blood had been present in the urine several times. She was *very nervous*, which seemed to account for the rapid heart action, which was 140, perfectly regular, with all beats coming through to the wrist. A rate of over 120 was maintained for a number of days. She was



emotional and cried a good deal. The urine obtained by catheter always contained red blood cells, which cystoscopy demonstrated came from the kidneys. The amount and gravity of the urine was normal and there was no nitrogen retention, though there was some diminution in the phthalein output. *Typical leg pains were present after antisyphilitic treatment was started; these focal reactions are very suggestive. Pupils regular, equal and actively mobile. On admission the knee-jerks were much diminished and unequal; five months later they were absent. Ankle-jerks were present at first, but disappeared several months before the knee-jerks became absent.* Blood Wassermann was positive; spinal fluid Wassermann was positive; colloidal-gold luetic curve.

The pains due to lesions in the upper segments of the cord are less common and more difficult of recognition. They may be very severe and "colicky," or the patient may experience a sense of constriction, as though a rope or a band were drawn about the chest.

CASE V.—M. P., aged thirty-seven years. Eleven years previously and seven years after his initial lesion he began experiencing *severe pains through the lower part of his chest and the upper part of the abdomen*, more marked on the right side. Electricity failing to give relief the right nipple and a small amount of mammary gland immediately surrounding it was removed. The pain persisting, with commendable perseverance, though with questionable judgment, the surgeon removed the other nipple. Eleven years after the pain started he was an advanced tabetic.

CASE VI.—D. J., a woman, aged thirty-six years, complained of *pain under the left scapula*. This was diagnosed as pleurisy, and some relief seemed to follow the application of adhesive straps. It was subsequently present along the right side as well. It finally became more marked and was then described as a sense of constriction, as though something were tied about the chest. Soon the development of gastric crises and the loss of the reflexes placed the diagnosis on a firm basis.

Very distressing are the so-called crises affecting various viscera—stomach, kidney, heart, larynx, etc.

CASE VII.—I have at present a patient, aged thirty-two years, who illustrates the varying nature of the crises. On two occasions, about eight months ago, he was *awakened at night with severe pain "about the heart"—the pains extended into the left arm*. Within a few weeks he had a *pain in the region of the liver*, beginning gradually but soon becoming so severe that morphine was required. This was accompanied by *pain in the right arm*. The next attack affected the precordial region and the left arm. The succeeding one, which was confined to the *hepatic area*, was preceded for a couple of days by

pains in the right arm. In the last attack but one the pain was again in the left side at about the level of the fifth and sixth ribs. The most recent attack was very severe and confined to the region of the right costal border. A positive diagnosis of gall-stones was made by several physicians who saw him, and an operation was urged. In addition to these severe attacks he describes a "soreness inside" across the chest, and has himself observed that the skin opposite the third, fourth and fifth ribs is less sensitive to touch than above and below this area. In two attacks it was observed that the abdominal muscles were held very rigidly, but no tenderness could be elicited; in other attacks the abdomen was soft. The pains which came in waves were very intense. *The pupils were normal.* The deep reflexes were absent; both blood and spinal fluid Wassermanns were positive.

Gastric crises are the most common type and were present in 10 per cent of this series. When they precede the pupillary changes and the loss of the deep reflexes they are very difficult of diagnosis. The moderate leukocytosis that has been present in several of our cases adds to the difficulty. *Severe abdominal pain, accompanied by vomiting but without abdominal rigidity or localized tenderness, should suggest tabes.* The crises are generally described as beginning without prodromata; severe attacks of pain and vomiting lasting for a number of days. In a few cases I have seen the attacks were preceded by two or three days of discomfort and drawing sensations in the lower part of the back, described by one woman as similar to labor pains. While the severity of the pains may suggest gall-stones the most common mistake is to diagnose some stomach lesion. Sufferers from this condition have often been operated upon not once but several times.

CASE VIII.--L. O., aged thirty-six years, who had a chancre years before, was admitted to the Hartford Hospital about ten years ago complaining of *severe abdominal pains and persistent vomiting* of several days duration. Several years before, when he had the same symptoms, he was operated for suspected gall-stones in a hospital in Brooklyn, but none were found. Fifteen months later he was operated in New York for adhesions; six months later, his symptoms persisting, he was again explored in another New York hospital. As he appeared to have an open season for laparotomies the year around it is quite natural that we should emulate the example of the distinguished New York surgeons. Accordingly *the abdomen was opened for the fourth time*, revealing a mass of adhesions.

But this was years ago; today, with the assistance furnished by the roentgen-ray, the blood Wassermann and the spinal-fluid examination such mistakes would not occur. Of course, the tabetic is liable to any other malady to which man is heir, as a recent

patient demonstrated. He had severe upper abdominal pain and the typical signs of tabes, but a negative blood and spinal fluid. Antisyphilitic treatment did not relieve him, so the abdomen was opened and a carcinoma of the gall-bladder was found.

Laryngeal crises are fortunately very rare and occurred in but one of this series.

CASE IX.—M. E., aged thirty-nine years, had very severe attacks of *choking*, first coming on after drinking to excess. He would awaken at night choking and would become deeply cyanosed. All accessory muscles of respiration were called into play. The pulse was of good quality in one attack and very faint in another one. The attack would last from a few minutes to an hour. During the severest attack in 1913 artificial respiration was resorted to, and it seemed as if death would take place at any minute. He had been suffering very severely prior to the time from leg pains and had been given a number of hypodermics of morphine. It is possible that this was a factor, as *tabetics are occasionally met with who stand morphine very badly*. Several years ago I almost lost one patient following the administration of a small amount of codein and morphine for leg pains.

One patient seen several years ago was subject to very severe attacks of pain that were localized in the symphysis pubes. A recent case complains of a pain that "comes quickly" in the region of the sacrum; it extends forward across the lower abdomen, and the patient then experiences the desire to go to stool. An enema, even though no bowel movement results, gives relief for several hours.

Severe pain referred to the kidney, designated as a renal crisis, occurred in 3 patients. In one man, who also had gastric crises, the pain radiated to the testicle. There may be no radiation, the pain suddenly comes on with great intensity, persists for a few minutes and then subsides momentarily, only to recur with stabbing intensity. In 1 very typical case I could elicit no tenderness.

CASE X.—One of the most interesting cases of this series was a man, aged twenty-two years, referred to me by Drs. Kingsbury and Hutchison, to whom I am indebted for the early notes in the case. He complained of *severe pain in the right flank radiating to the penis*; also hematuria and increased frequency, with difficulty in starting the stream. He had had two similar attacks during the two years preceding, and during one of which there had been considerable albumin in the urine. *The pupils and the knee-jerks were normal* and the roentgen-ray for kidney-stone was negative. Cystoscopy by Dr. T. N. Hepburn, who made the following resume of his findings:

"It is evident that this man's kidneys are functioning equally

and apparently normally, as shown by their excretion both by indigo carmin and phthalein. His marked *bladder trabeculation* suggests some spinal-cord pathology. The history of urine spasm during his attacks of renal colic with swelling of the extremities suggests that these times he has acute nephritis with hemorrhage. In view of the fact that the ureters admit No. 7 catheters without difficulty under anesthesia and the roentgen-ray being negative, there seems to be no calculous pathology. With his marked bilateral hemorrhages and his normal renal function the diagnosis of essential hematuria seems very possible. His bladder, nervousness with intermittent bladder spasm, suggests the true bladder tic. My personal diagnosis is that he has essential intermittent hematuria with blood-clots forming in his ureters, causing ureteral spasm and secondary bladder spasm which causes his incontinence. My treatment should depend largely upon the spinal-fluid examination and Wassermann."

Both the blood Wassermann and spinal-fluid Wassermann were positive and the patient showed the paretic colloidal-gold reaction. *Two years later the pupils were immobile and the knee-jerks had disappeared.*

This was 1 of the 4 cases in which the infection appeared to have been prenatal.

Drs. Hepburn and Spillane have cystoscoped all of our recent cases and the bladder trabeculation has been found almost without exception. The trabeculation may be due to hypertrophy of the muscles of the bladder resulting from an attempt to overcome the distention that takes place because the sensory nerves of the bladder that initiate the act of micturition are degenerated. We, however, do not feel that tabes is the only cord lesion that will produce trabeculation.

One never ceases to marvel at the extensive pathology that may be present without causing symptoms. I vividly recall a man, brought to the hospital some years ago, because of a minor injury, who had an aneurysm as large as a child's head. He had stoutly maintained that he had no symptoms and refused to remain longer than was required for his scalp wound. Many have seen patients with extensive pulmonary tuberculosis who had at no time any symptoms of this disease. The following case illustrates the necessity for a complete examination irrespective of the patient's complaint and demonstrates that extensive changes of a permanent nature may be present in the nervous system notwithstanding the complete freedom of symptoms.

CASE XI.—C. E., *a robust man*, aged forty-four years, who looked the picture of health, *came to me for an examination of his lungs.* Several years previously he had tuberculosis with bacilli in the sputum. He had been free from symptoms for some time, though

he was recently advised by an eminent specialist in tuberculosis that it was too soon for him to resume his work. He desired the examination in order that he might secure a pension as a Spanish War veteran. He had a very few fine rales on coughing at the apices; they did not, however, suggest activity. His blood-pressure was considerably elevated and there was a heavy trace of albumin in the urine. There was left external strabismus. The pupil of the left eye was normal; that of the right eye was immobile. Both knee- and ankle-jerks were absent. Blood and spinal-fluid Wassermann was four plus and a luetic colloidal-gold curve.

Contrast with this asymptomatic case with definite physical signs, the following case recently seen in whom the symptoms are marked, but the classical physical signs lacking.

CASE XII.—A man, aged sixty-one years, who had an initial lesion twenty odd years ago, complains of severe pains in the legs below the knees, extending down to the ankles. Walking up or down grade makes the pain almost unbearable. He also has sudden sharp pains in the thighs. At night he has a drawing sensation in the feet so marked as to necessitate his getting up to stretch them. This he does by pressing them against the floor or the foot-board of the bed. He usually goes all day with no desire to void. Notwithstanding that *both knee- and ankle-jerks are present and the pupils react to light* his symptoms must be attributed to changes in the posterior nerve roots.

There is still another type of a case entirely symptom-free, and in addition with an entirely negative physical examination, except for a persistently positive blood Wassermann. This is the pre- or potentially tabetic case, which if promptly recognized and adequately treated can often be cured. The following is an example:

CASE XIII.—R. J. was referred for arsphenamine treatment because of *gangrene of the hand*. This improved promptly under injections of arsphenamine, but *the Wassermann test on the blood after fifteen treatments, with a course of iodide and mercury, was still positive*. A patient whose Wassermann cannot be influenced by a course of eight to ten injections of arsphenamine should always have the *spinal fluid* examined, as it will be found positive in many instances. In this case it was reported *positive in 0.5 cc.* The physical examination may be entirely negative or the degree of reaction of the pupils to the light test may be slightly diminished and the deep reflexes perhaps slightly increased.

*Occasionally the blood Wassermann may become negative after intravenous treatments, but a positive reaction will be found in the spinal fluid even though there be no symptoms or physical signs pointing to involvement of the nervous system. Accordingly a spinal-fluid examination should be made in all cases at the conclusion of the second course of injections.*

**Important Points in the Physical Examination.** The Argyll-Robertson pupils, reacting to accommodation but not to light, and the completely immobile pupils, often unequal and irregular in outline, are the usual findings. It should be more generally known that occasionally *one or both pupils may be normal*, especially early in the disease. In 25 per cent of our cases the pupils were normal, though 4 patients, who were followed for several years, subsequently showed the changes characteristic of the disease. In 2 instances one pupil was normal. It is probable that a sluggish and diminished response to light regularly precedes immobility. Quite commonly one sees pupils in which the reaction to light starts promptly but ceases just as it gets under way. In some instances this appears to be due to the adhesions of a previous iritis. Two cases presented a paradoxical reflex when first seen. In 1, six years later, the pupils had become small, irregular and immobile. The other had typical Argyll-Robertson pupils at the end of two years. Save in one instance following hemiplegia, I have never seen the light reflex return. In this case the return was only partial and did not persist.

*The knee-jerks* were both absent in 60 per cent of our cases, diminished or unequal in 19 per cent and in 6 cases (10 per cent) *much increased*. It is quite likely that the cases showing greatly increased knee-jerks have some involvement of the lateral column as well as the posterior. Both columns were probably involved in Case I, as his knee-jerks were very active when first seen. The nature of the early pathology is such as to suggest that increase of the reflexes may occur more frequently than has generally been assumed. Two patients who exhibited increased knee-jerks several years ago, and who have had a good deal of treatment, now show normal reflexes. Another patient who had increased knee-jerks several years ago has none at present. *The ankle-jerk* is not recorded in all of the cases, but it *was absent in 3 in whom the knee-jerk was present*. In 2 instances the knee-jerk could not be obtained though the ankle-jerk was present. In 1 definite case of tabes and in 1 probable case both knee- and ankle-jerks returned following treatment. A careful examination will often reveal areas of anesthesia, most commonly about the feet. Two patients with girdle pains had an anesthetic band, two inches wide, across the chest. The blood Wassermann was positive in 65 per cent of 54 cases tested. In 38 cases the spinal fluid was examined and the Wassermann was positive in 66 per cent. In a few instances the spinal fluid was positive when the blood was negative. In one adult with a prenatal infection both blood and spinal fluid Wassermann were negative. Another case had repeated examinations made of blood and fluid and only once was a weak positive obtained in the spinal fluid. As the colloidal-gold test was only made in the cases seen recently, they are too few to analyze. We have several times obtained a paretic curve in patients exhibiting none of the symptoms of paresis.

**Differential Diagnosis.** *Severe pains suggestive of tabes may be due to spondylitis or to faulty posture.* This should be suspected in all atypical cases, especially when the blood and spinal-fluid examinations are negative. Moreover, the tabetics digestive symptoms may be due to ulcer rather than to gastric crises. Occasionally *foci of infection*, especially peridental abscesses, may be wholly or in part responsible for severe leg pains. One patient who had been quite free from lightning pains for some time suffered a great deal from their recurrence following the removal of a number of badly abscessed teeth. Several years ago I mistook a case of alcoholic neuritis in a syphilitic for tabes.<sup>1</sup>

It is stated that fixed pupils may be due to cerebral arterial sclerosis, not the result of syphilis. Such cases are uncommon and difficult of diagnosis, as a negative Wassermann test, of course, does not exclude syphilis. *It is apparent that the diagnosis of tabes does not rest on any one set of data; only by a consideration of the symptoms, the physical signs and the blood and spinal-fluid examinations can we arrive at our diagnosis.*

**Treatment.** (a) GENERAL. Before proceeding with the discussion of spirocheticidal remedies and the methods of administration it is perhaps advisable to refer to a number of important points in the management of these patients that are sometimes overlooked. In the first place *the posture of the tabetic is usually faulty.* He is prone to assume the attitude so characteristic of all asthenic states, namely, abdominal protrusion with thoracic recession, the so-called "debutante slump" resulting in increase of the lumbosacral curve and a tilting forward and downward of the pelvis. The abduction of the feet that occurs with increasing unsteadiness is usually associated with marked pronation and loss of the longitudinal arch. The usual corrective exercises and appliances for these conditions should be prescribed. Patients exhibiting marked ataxia should be given *reëducational exercises.* *Hydrotherapy* requires no elaborate apparatus, and is especially helpful in some cases. Careful search for foci of infection should be made, as they are sometimes a factor in causing pains. The teeth and gums should receive the necessary attention *before specific treatment is instituted.*

(b) SPECIFIC. It is perhaps unnecessary to state that the immobile pupil and absent knee-jerk do not in themselves call for anti-syphilitic treatment.

I first saw Mr. B. H. in 1909, when he was aged seventy-four years. He presented the usual signs of advanced tabes, yet with no symptoms. The absent reflexes had been discovered years before. The blood and spinal fluid were both negative a few

<sup>1</sup>The question of "pseudo-tabes" was raised in Case III, who was somewhat alcoholic. A neuro-syphilitic might of course have alcoholic neuritis but the pains and tenderness commonly met with in neuritis were absent, while the bladder trabeculation so common in tabes dorsalis was present.

years later. I have seen him occasionally since then, the last time a few months ago, when he was "holding his own" pretty well, notwithstanding his eighty-five years. Insofar as I know he has never had any active antisyphilitic treatment.

It is impossible to formulate a plan of treatment suitable to all cases. Individualization, always important, is particularly so with this group. It is rather generally believed that fewer of the nervous reactions occur if mercury and iodide are given for a short time, three or four weeks, before arsphenamine is started. The frequency of treatment depends on the results to be expected. If we believe we can annihilate our enemy by assault, as is possible when dealing with a primary lesion, a few intravenous injections may well be given at two- or three-day intervals. When, however, the enemy through long years of preparation is well entrenched the assault is ill-advised; much more can be gained by a prolonged siege. Accordingly, in tabetics we will do well to give injections at weekly intervals for the first two months, during which time iodides and mercury either by inunctions or injections may safely be administered if one be on the alert for evidences of renal intolerance. Another month of mercury, then a rest period of a month or two, and then another course of arsphenamine injections, are safe procedures to follow. *When the symptomatic response to intravenous treatment is unsatisfactory, or when we are not successful in reducing the Wassermann or colloidal-gold reaction of the spinal fluid, intraspinal treatment should be used.*

The indications for intraspinal treatment in tabes may be found outside the nervous system as when a serious cardiovascular lesion makes the repeated intravenous injection of arsphenamine a hazardous procedure. I believe it is also desirable to institute both intravenous and intraspinal treatments as soon as possible in patients exhibiting a paretic colloidal gold curve unaccompanied by paretic symptoms. The so-called "paretic curve" is probably indicative of serious parenchymal involvement but not necessarily paresis. A limited experience in the treatment of paretics has been rather discouraging.

The original Swift-Ellis method is generally conceded to give the best results. The reactions are less than with any of the modifications or substitutes that have been suggested. After a thorough trial of the fortification method suggested by Ogelvy, Fordyce has gone back to the original and simpler technic. It is not my brief to argue the *rationale* of intraspinal treatment; this has been done by far abler men. The fallacy of the claim that the good results are due to the drainage incident to the treatments has recently been shown by Fordyce,<sup>4</sup> Stokes,<sup>5</sup> and Osborne and Keidel and Moore,<sup>6</sup> all of whom obtained prompt clinical and serologic improvement when intraspinal treatments were substituted for drainage. Solomon, who for years advocated only intensive intravenous treatment, now employs intraspinal therapy in suitable



cases. The recent work of Dandy,<sup>7</sup> with cerebral pneumography, has shown that when there are no adhesions at the base of the brain all the deep and superficial spaces may be reached by the intraspinal route. It may be found advisable in certain cases to have a cerebral pneumograph made before employing intraspinal treatment to determine the patency of the spaces. It is a mooted point whether the injection of an irritating substance subdurally increases the permeability of the choroidal plexus. As there is some evidence to suggest that this may occur we have recently been giving our intravenous injections within an hour after the intraspinal, the serum for the latter having been obtained the day previously from another patient. As yet we have no opinion as to whether this reversal of treatments is of any special value. The method, however, is quite as well borne as the original technic.

How many treatments shall we give the tabetic? Two or three courses may be if he is fortunate in having the diagnosis made at the first inception of symptoms, or better still by spinal-fluid examination when asymptomatic and in the pretabetic state. When not recognized until the pathology is extensive, after the first two or three courses, he will probably require occasional treatments all his life. *Even though there be advanced nerve degeneration it often happens that there are some neurons still intact and capable of carrying on with assistance.* Active treatment in these cases will sometimes restore the latter to functional efficiency. This is occasionally demonstrated by the improvement in the vision of patients who from the ophthalmoscopic standpoint have optic nerve atrophy. The degree of improvement that sometimes obtains even when the treatment is deferred until many years after the onset of symptoms is very gratifying. The first case mentioned in whom treatment was not instituted until twenty-five years after the chancre and ten years after the beginning of symptoms has greatly improved in his general health. He no longer has pains, though he occasionally has numbness in his feet at night. During the past eight years he has received thirty intravenous and twenty-six intraspinal treatments. He has worked steadily since the treatments were started and has never been absent from his work through illness, except for a few days at the time of treatment, a record that is not equalled by anyone in the office where he is employed. He is still incontinent at night, but less so. He walks much better and each summer works daily in his garden. The knee-jerks, which were greatly increased when treatment was started, are now normal. The blood Wassermann is negative; the spinal fluid still shows a positive Wassermann in 0.5 cc and a weak leucic curve.

Even more striking were the results obtained in Case III, the woman who could not stand alone. Reëducational exercises were started at the same time that antisyphilitic treatment was instituted. As she had a paretic colloidal-gold reaction, though without any

symptoms of paresis, she was placed upon combined intravenous and intraspinal treatment, with mercury inunctions and potassium iodide. In less than two weeks she was beginning to walk, and in one month the knee and ankle reflexes had returned, though the pupillary reflex did not return. As she had a chronic tuberculous process at the apices with bacilli in the sputum, she was sent to the state sanatorium, returning to the hospital every two or three weeks for treatment.

She was given fifteen intravenous and seven intraspinal treatments in addition to several months of mercury inunctions. The spinal fluid Wassermann at first was positive in 1 cc. This soon became positive with smaller amounts (0.4 and 0.2). It is now, one year later, negative with 2 cc (both plain and cholesterinized antigens). The first colloidal gold was 555443100. The most recent report was 554330000. The blood Wassermann, at first strongly positive, is at present plus minus. The only symptom mentioned at present is an occasional drawing sensation in one of the toes.

After observing the marked improvement in her general condition and gain in weight since going to the sanatorium, one wonders if tabetics might not hasten their recovery by "taking the cure" while undergoing specific treatment. Though she is symptom-free, she still has a positive Wassermann in the spinal fluid and the paretic curve persists after fifteen intravenous and seven intraspinal treatments.

*We should never lose sight of the fact that we are treating a patient as well as a disease.* The number of treatments depend upon three things: (1) The effect on the symptoms, (2) the effect on the Wassermann reaction and (3) the effect on the patient. *Continue the treatments until the symptoms subside and the Wassermann is negative if the general condition of the patient shows improvement.* When after several courses of arsphenamine injections the general condition is not satisfactory, though the symptoms may be less, always consider the possibility of an intercurrent infection, especially tuberculosis. Discontinue all antisyphilitic medication for several months, get the patient outdoors and employ all possible aids to build him up. With an improvement in his general resistance the Wassermann may become negative.

**Summary.** 1. It is generally believed that infection of the nervous system takes place very early during the secondary stage, at the time of maximum spirochetal mobilization.

2. While it has been estimated that 25 per cent of poorly treated syphilitics subsequently develop syphilis of the nervous system, less than 3 per cent of cases treated intensively during their primary stage show changes in the spinal fluid at the end of treatment.

3. A spinal-fluid examination should be advised at the conclusion of the second series of arsphenamine treatments. It is imperative in all "Wassermann-fast" cases.

4. A complete history is of the utmost importance in detecting early cases. It will sometimes be "positive" when the serology is negative. Next to darting pains, bladder symptoms, especially unconscious distention, appear to be of special significance.

5. The pupils may be normal, the deep reflexes present, yet the symptoms may be due to early meningeal changes about the posterior nerve roots.

6. Arsphenamine intravenously, with mercury and the iodides, will prove sufficient in many cases, especially the early ones.

7. When the symptomatic or serologic response to intravenous treatment is unsatisfactory, or when a grave cardiovascular lesion coexists and makes frequent intravenous treatments hazardous, intraspinal treatments should be instituted.

8. Serious results are more liable to follow repeated series of intravenous injections than properly administered intraspinal treatments.

9. The amount of treatment should not be determined solely by the Wassermann test; the general condition of the patient is deserving of more consideration than it often receives.

**Conclusion.** The rational treatment of tabes should include not alone the administration of antisyphilitic remedies but the employment of all known agencies for the improvement of the general health, together with periodic examinations of the patient, his blood and his spinal fluid throughout his life.

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#### THE QUESTION OF THE USE OF ANESTHESIA IN LUMBAR PUNCTURE.

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WHETHER or not anesthesia, either local or general, should be used in lumbar puncture is a subject upon which some little diverg-

ence of opinion exists. Inasmuch as the employment of a general anesthetic is not without an element of danger, and adds to the risks of an operation which without it has a mortality certainly no higher than that attributable to most general anesthetics themselves, it would seem that the necessity for their use would be a point of some importance. In the absence of any detailed treatise on this phase of the operation of rachientesis it may be of some practical value to draw a few conclusions as to the factors that would decide the operator in his employment of anesthesia in the procedure.

**General Anesthesia.**—Most authorities of extensive experience, among them Ravout,<sup>1</sup> Neal and DuBois,<sup>2</sup> and Sophian,<sup>3</sup> are of the opinion that general anesthesia is not needed. Quincke,<sup>4</sup> in his original and masterly description of the operation, stated that anesthesia was not essential, with the exception of very rare cases of delirium of a violent type. Howell,<sup>5</sup> however, believes a general anesthetic necessary in children owing to the danger of a sudden movement on the part of the child causing breaking of the needle. Landon,<sup>6</sup> although he does not generally employ anesthetics, sees no objection to their use. Concetti<sup>7</sup> does not administer chloroform in most cases, but has had recourse to it in very nervous children who were greatly agitated, especially when there was marked rigidity of the spinal column. Jelliffe and White<sup>8</sup> have made use of anesthetics if marked tenderness or opisthotonos is present.

In an experience of over 1000 lumbar punctures performed in a variety of meningeal conditions in both children and adults the writer has only seldom seen patients in whom a general anesthetic was required. It is very rare that a child is delirious and restless enough as to require anesthesia. In fact, it may safely be said that if someone is at hand who can properly hold the patient it can almost always be dispensed with. The pain accompanying the introduction of the needle is so transient, and the time required to penetrate to the subarachnoid space of a child is so short (a few seconds), that it seems scarcely justifiable to make use of a general anesthetic. Likewise in adult patients if the operator is skilful the operation is also only a matter of but a few moments. With the proper type of needle and with a sharply beveled point the introduction is but momentarily painful. If the physician is unfamiliar with the procedure or the puncture is difficult, due to anatomic configuration, it may be advisable to resort to local, but surely not to general anesthesia.

<sup>1</sup> Translated by O. Mulot: *Am. Med.*, 7, 563.

<sup>2</sup> *Am. Jour. Dis. of Children*, 9, 1.

<sup>3</sup> *Epidemic Cerebrospinal Meningitis*, St. Louis, 1913, p. 206.

<sup>4</sup> *Die Technik der Lumbalpunktion*, Berlin, 1902.

<sup>5</sup> *Clin. Jour.*, London, January 15, 1913.

<sup>6</sup> *Lancet*, April 16, 1910, p. 1057.

<sup>7</sup> *Annales de médecine et chirurgie infantile*, 1899.

<sup>8</sup> *Modern Treatment of Mental and Nervous Diseases*, Philadelphia, 1913, p. 280.

General anesthetics are obviously contraindicated in rachientesis in patients who are very ill, giving the procedure an element of risk proportionate to the condition of the patient and to the severity of the disease in which it is employed. In this connection consideration and due weight must be given to the possible after-effects of the anesthetic on the heart and kidneys and the immediate effect on the heart, the respiration and the blood-pressure, all of which may be already affected by the particular disease in which the operation is performed. Then again the recognized danger of general anesthesia in patients with atheromatous arteries, or in those with diabetes or brain tumor, must not be forgotten.

In many cases of meningitis the mental apathy or stupor of the patient renders anesthesia entirely unnecessary. Even in the violently delirious it is evident that anesthetic cannot be used for each daily puncture. In some it may be demanded for the first puncture or two, but then must be dispensed with.

In very nervous adults not acutely ill on whom the operation is to be performed, for diagnostic or therapeutic purposes, a general anesthetic is practically never required. If needed local anesthesia by cocain will usually be sufficient. In rachientesis for spinal anesthesia it is obvious that a general anesthetic is not to be considered.

There are only a few instances in which it may be employed with advantage. It may at times be necessitated by exceedingly delirious and violent adults who are so robust that they cannot be controlled by any other means. Certainly, the struggling which in some instances follows an attempt to hold such patients will place as much strain on the heart and influence the blood-pressure more than the cautious use of an anesthetic. An additional danger is also thereby avoided, the possibility of the needle being broken. Under such circumstances one may have at times to resort to an anesthetic. Likewise in the violently insane anesthesia may be required.

We have never found it necessary to employ anesthesia for either opisthotonos or marked hyperesthesia in meningitis patients. Ashhurst<sup>9</sup> believes it should be used in cases of tetanus. Certainly, lumbar puncture is rendered much easier and the operation is more satisfactorily completed when a light chloroform anesthesia is used.

As to the general anesthetic to be employed when such is demanded, Sophian<sup>10</sup> and Ker<sup>11</sup> believe that chloroform is the best. Certain authors make use of ether. Thus, Nissl<sup>12</sup> employs the latter in lumbar puncture in the insane. Bloodgood and McGlannon<sup>13</sup> recommend that ether or nitrous oxide and oxygen should be used

<sup>9</sup> *Am. Jour. Med. Sc.*, 1913, 146, 92.

<sup>10</sup> *Loc. cit.*

<sup>11</sup> *Infectious Diseases*, London 1909, p. 509.

<sup>12</sup> *Jour. Nerv. and Ment. Dis.*, May, 1907, p. 312.

<sup>13</sup> *Musser and Kelly's Handbook of Practical Treatment*, Philadelphia, 1911, 1, 604.

to secure relaxation if opisthotonos is marked, as in cases of tetanus. We believe with Sophian and Ker that chloroform is preferable. The patient can be much more rapidly anesthetized than with ether, the stage of excitement is not so marked, the quantity of the anesthetic required is very much less and the slight degree of anesthesia, which is just sufficient for the operation, is readily obtained. More-over the after-symptoms are not nearly so troublesome. One must, of course, bear in mind that the contraindications to chloroform, especially in patients with fatty degeneration of the myocardium, appertain here as elsewhere. In order to avoid the possibility of any accidents the anesthetic should be given slowly, well diluted and the patient put under gradually.

It is often possible to avoid the use of a general anesthetic in delirious, excitable or very nervous patients by giving two hours before puncture a hypodermic injection of morphine and atropine sulphate in amounts proportionate to the age. For adults, morphine sulphate gr.  $\frac{1}{4}$  and atropin sulphate gr.  $\frac{1}{120}$ ; for children in proportionate doses. Ker makes use of similar injections, supplemented by the administration of 2 oz. spiritus frumenti fifteen minutes before operation. A somewhat smaller dose (3ss to 5ij) may certainly be given in many instances, more especially to those accustomed to the use of alcohol.

Many patients with meningitis may be kept quieter throughout the operation by using what Sophian terms "water anesthesia," having the patient sip water through a straw during the procedure.

In puncturing patients in whom resistance is expected, or who are so nervous or delirious that it is anticipated that the proper position for operation cannot be maintained once the introduction of the needle has been started, it is of invaluable assistance to secure them in the following manner: The diagonally opposite ends of a full-sized bed-sheet are taken hold of by two persons and twirled into the form of a rope. With the patient in the proper posture on his side this prepared sheet is placed under his knees and then the two free ends are drawn upward, flexing the lower limbs well up toward the abdomen. The ends are then crossed and used to encircle the arms above the elbows, and from there are brought over the shoulders and knotted securely in the back. Many patients who would otherwise require several assistants to hold them or a general anesthetic may be satisfactorily treated when secured in this way.

**Local Anesthesia.**—The question of local anesthesia is of much less relative importance than that of general anesthesia. Nevertheless, under certain circumstances the injudicious employment of some local anesthetics, especially in meningitis, may further complicate the subsequent treatment of the case. While many writers, among them Porter,<sup>14</sup> Stewart<sup>15</sup> and Jelliffe

<sup>14</sup> Southern California Practitioner, September, 1912.

<sup>15</sup> Diagnosis of Nervous Diseases, New York, 1912, p. 403.

and White,<sup>16</sup> advocate the more or less routine employment of local anesthetics either by means of cocain or a spray of ethyl chloride, others restrict their use to particular types of cases. Gray<sup>17</sup> introduces 10 to 20 minims of a 3 per cent solution of eucain under the skin at the site of puncture as a preparation for rachientesis in spinal anesthesia in children. Barker,<sup>18</sup> however, in performing the operation for the same purpose in adults, does not find this preliminary preparation necessary. Howell,<sup>19</sup> Clergier,<sup>20</sup> Neal and Du Bois<sup>21</sup> do not believe any local anesthetic required. Duffos<sup>22</sup> allows a little ether which has been used to wash the region to remain and evaporate. Rosenthal<sup>23</sup> finds the operation particularly facilitated by a progressively deep infiltration with 0.5 per cent solution of cocain two minutes before puncture.

We have rarely found it necessary to utilize any local anesthetic in our patients. In children the subarachnoid space is relatively superficial, varying in depth from 3 to 4.5 cm., depending on the age. For this reason when the back is well arched and the operator experienced the needle penetrates the dura almost immediately after it passes through the skin. The pain is therefore very transient, the skin and dura being the only sensitive tissues traversed. While local anesthesia has the advantage of diminishing somewhat the pain of the skin puncture, it cannot affect that of the deeper tissues. Its disadvantages, which are mentioned below, in most instances offset this slight diminution of pain. It may safely be said that in young patients it is rarely required with the exception of those on whom the procedure is performed preliminary to the administering of a spinal anesthetic. Under such conditions a superficial or progressively deep infiltration with cocain or one of its derivatives may be serviceable in enabling the operator to better keep the confidence of his patient during the subsequent operation.

In adults local anesthetics are demanded only in exceptional instances. When only one puncture is to be performed in a patient not acutely ill the decision rests with the physician. In very nervous individuals it may be required to avoid a general anesthetic. It often impresses the patient as a more humane method of procedure and must be considered accordingly under such circumstances.

In many cases of meningitis the mental state of the patient makes any anesthetic unnecessary. In all instances in which repeated punctures are to be employed, as in the various types of meningitis, poliomyelitis, etc., the repeated use of cocain, either superficially or deeply, is open to the decided objection that it may inflame the tissues and thus open the way to infection, interfering seriously with subsequent treatment.

<sup>16</sup> *Loc. cit.*

<sup>17</sup> *British Med. Jour.*, 1, 665.

<sup>18</sup> *Thesis of Paris*, 1901-1905, Paris, 1905.

<sup>19</sup> *Thesis of Paris*, 1901-1902, No. 7.

<sup>20</sup> *Paris médicale*, August 12, 1916, p. 142.

<sup>21</sup> *Lancet*, September 25, 1909, p. 913.

<sup>22</sup> *Loc. cit.*

<sup>23</sup> *Loc. cit.*

Ethyl chloride is particularly objectionable as a local anesthetic in both children and adults if the patient's spine is at all hyperesthetic. Moreover, by hardening the skin over the site of puncture it interferes with the clearly defined sensation of touch which is so important in starting the introduction of the needle in the proper direction. In adults it is practically useless because its transient anesthetic effects are exerted upon the cutaneous tissues, which are the source of only a small part of the pain. Adult patients experience most discomfort from striking the spinous processes, the lamina or the nerve roots of the cauda equina, as well as when the needle passes through the ligaments and the dura. Progressively deep infiltration with cocain is the only method which even noticeably alleviates the pain of the operation. Finally, it may be said that local anesthesia is rarely required by one skilled in the technic of the operation.

**Summary.** 1. General anesthesia is very rarely required in performing the operation of rachientesis. A child is seldom delirious and restless enough as to require a general anesthetic, and it does not seem justifiable to make use of one in an operation which can be so quickly performed and in which the pain is so transient. Likewise in adult patients, if the operator is skilful only a few seconds are required to penetrate to the subarachnoid space, and the pain is only momentary.

2. General anesthetics are very much contraindicated in persons who are seriously ill, giving the procedure an element of risk proportionate to the condition of the patient and to the severity of the disease in which it is employed. The immediate effects of the anesthetic upon the heart, the respiration and the blood-pressure, and the remote effects upon the heart and kidneys, all of which may be involved by the particular disease in which the operation is performed, must not be forgotten.

3. The contraindications to anesthesia in patients with atheromatous arteries, or in those with diabetes or brain tumor, appertain here as elsewhere.

4. The only classes of patients in whom general anesthesia may be demanded are those who are exceedingly delirious and robust adults who cannot be controlled by any other means. The struggling which ensues on any attempt to hold such individuals will place as much strain on the heart and influence the blood-pressure more than the cautious use of an anesthetic.

5. In puncturing insane patients under similar circumstances general anesthesia may at times be required.

6. Rigidity of the back and opisthotonos, unless it is so extreme as to prevent the introduction of the needle, are not an indication for a general anesthetic.

7. Likewise in very nervous patients general anesthesia is not necessary. A local anesthetic will be sufficient.



8. When demanded the anesthetic which it is preferable to use is chloroform. The patient can be much more rapidly anesthetized than with ether, the stage of excitement is less and the quantity of the anesthetic required is very small. It should be given very slowly, well diluted and the patient put under only lightly.

9. In many delirious and excitable or very nervous persons the use of a general anesthetic may be avoided by injecting hypodermically, two hours before the operation, morphin sulphate gr.  $\frac{1}{4}$  and atropin sulphate gr.  $\frac{1}{120}$  (for an adult). This may be supplemented, especially in the case of alcoholics, by a dose (5j to 5ij) of spiritus frumenti fifteen minutes before puncture.

10. Water anesthesia, allowing the patient to sup water during the operation, is helpful in keeping some patients, especially those with epidemic meningitis, quiet during the treatment.

11. In puncturing patients in whom resistance is expected, and who are so nervous or delirious that it is anticipated the proper position cannot be maintained, it is of invaluable assistance to secure them by means of a sheet twisted into the form of a rope and applied as described above.

12. Local anesthetics are rarely required in children with the exception of those in whom rachientesis is performed preliminary to the administration of a spinal anesthetic.

13. In adults local anesthesia is needed only in exceptional instances. When only one puncture is to be performed the decision rests with the operator. It often impresses the patient as a more humane method of procedure, and must be considered accordingly.

15. *In all cases in which several punctures are necessary the repeated use of cocain, either superficially or deeply, is open to the decided objection that it may inflame the tissues and thus open the way for infection. Ethyl chloride is unpleasant if the patient's spine is hyperesthetic. Moreover, by hardening the skin over the site of puncture it interferes with that clearly defined sensation of touch which is so important in starting the introduction of the needle in the proper direction.*

## A CLINICAL REPORT OF TWO CASES OF AGENESIS (CONGENITAL PARALYSIS) OF THE CRANIAL NERVES.

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FROM time to time cases are encountered that present functional defects dependent upon arrested development of certain structures. Deficiency in development may affect more than one system of

the body, or it may be confined to structures involving one system alone.

The two cases I wish to report presented the rare condition of complete absence of function of certain cranial nerves; it was noted at birth, persisted, and was caused, I believe, by a lack of development of their nuclei of origin. This type of cranial nerve paralysis was first described by Möbius in 1892,<sup>1</sup> under the title of "Infantile Nuclear Atrophy." This observer collected 44 cases in which there was absence of function of the cranial nerves, the defect appearing in various combinations.

Möbius was able to prove the congenital origin of some of these cases, whereas in others the origin was uncertain; he believed, nevertheless, that all his cases were caused by a lack of development of the cells of origin of the cranial nerves or to defective vital endurance in these structures. Other observers since then have employed the term "aplasia of nerves" to denote the same condition.

Gowers<sup>2</sup> used the term "infantile oculofacial palsy" to describe defect of the facial and ocular nerves. I would suggest the term "agenesis of the cranial nerves" to describe a lack of development of these structures.

Although many different terms have been employed to describe the condition, the essential point is that the defect is a congenital one and is, therefore, present at birth, although in some instances nothing abnormal may be discovered by the parents until some time has elapsed, the true nature of this type of paralysis becoming thus confused with conditions that are acquired after birth and that are due to other causes.

In the cases reported here difficulty in using the lips for sucking first attracted attention, and paralysis of the facial muscles was noted almost immediately after birth.

H. M. Thomas<sup>3</sup> described similar defects occurring in two brothers. Fry and Kässack<sup>4</sup> also refer to the literature on the subject, and report the case of a girl, aged eleven years, in whom there was congenital paralysis of the seventh nerves on each side and an absence of lateral movements of the eyeballs, mandible and tongue, and a teratologic absence of the left breast.

A similar condition affected the brother of my second case. The tendency of congenital cranial nerve paralysis to occur in more than one member of the same family suggests the possibility of hereditary influence. True heredity, however, requires the transmission of the physical nature of the parent to the offspring, so that in this sense these defects cannot be regarded as being strictly

<sup>1</sup> München. med. Wehnschr., January, 1892, p. 17.

<sup>2</sup> Diseases of the Nervous System, 2, 197.

<sup>3</sup> Jour. Nerv. and Ment. Dis., 1898, 25, 571.

<sup>4</sup> Arch. Neurol. and Psych., December, 1919, 3, 638.

hereditary in nature, although the familial tendencies are quite marked.

The exact cause of developmental defects remains obscure and all explanations are inadequate. Nevertheless, the influence of deficient nutrition and disease, or of any other temporary abnormal condition of the parents, on the child before birth cannot be disregarded. Individual variations are well known. The physical difference between parents and offspring is due to the diversity of external influences.

Crouzon, Tretiskoff et Behague<sup>5</sup> have described the postmortem findings as affecting the nervous system in a case of familial external ophthalmoplegia, in which there was atrophy of the ocular nerves in association with an obscure type of fibrous meningitis, with integrity of the nucleus of the third cranial nerves, although these cells had undergone secondary degenerative changes. These authors admit that it is difficult to explain why the meningitis should be familial in character.

Whatever the true explanation may be it is obvious that more than one pathologic condition that may produce the congenital or familial type of congenital nerve paralysis must be present and the different combinations of cranial nerves may be found in different cases.

The clinical diagnosis must necessarily depend upon the discovery of the lack of function early in life, *i. e.*, shortly after birth, and the exclusion of other causes of cranial nerve paralysis.

In the following cases the upper portions of the face on each side were just as severely paralyzed as the lower portions of the face, therefore the lack of function conformed to the peripheral type of facial palsy.

Prognosis is necessarily unfavorable, and it would seem important to realize that such procedures as anastomosis with the hypoglossus for the restoration of function in the seventh nerves are useless.

CASE I.—Patient, aged thirteen years, consulted Dr. Frazier (who has kindly allowed me to refer to the notes) March 7, 1921, because of bilateral facial paralysis.

*History.* Father and mother were first cousins. Mother's first pregnancy ended in miscarriage. Patient was the second child; the third, fourth and fifth children are normal, but the sixth is affected by exactly the same condition as the patient, the defect having been noted at birth. The patient was born at full term without complications and appeared normal. The mother noticed, however, that the child had considerable difficulty in nursing, due to the fact that she could not control and use the facial muscles,

<sup>5</sup> Rev. neurol., 1921, No. 5, p. 488.

and particularly the lips, in sucking. The condition was disregarded, but when the child was about four months old it was noticed that she was unable to smile, and since then she has presented the appearance of complete bilateral peripheral facial paralysis. On examination by Dr. Frazier and myself nothing abnormal could be found except impairment of hearing on both sides, as tested by holding a watch close to her ear; she was unable to hear the ticking at a distance of five or six inches. Vision was normal and the mental and physical condition showed no abnormalities.



FIG. 1.—Case II. Showing patient's inability to blow out a lighted match because of not being able to pucker the lips due to muscular weakness.



FIG. 2.—Case II. Showing inability to elevate the eyeball when looking upward, and inability to move the facial muscles.

CASE II.—Patient, a girl, aged ten years, was admitted to the University Hospital Dispensary February 14, 1921. Mother died with gall-stones. Father, one brother and three sisters living and well. The father states that his first child died when two months old, the second died of injury when eight years old, and the third

pregnancy terminated in a miscarriage. Patient said to have been born at full term, the labor having been normal. Appeared healthy at birth but did not have a bowel movement for the first four days, a condition that was attributed to paralysis of the intestine, and was relieved by the insertion of a rectal tube, after which there was no further difficulty. Parents believed that the child's vision was normal at birth, and state that nothing abnormal was observed until she was one month old. At this time the eyes appeared to be "crossed," and she had some difficulty with her lips in sucking the bottle. About the same time it was noted that the child was unable to close either eye completely and that the facial muscles were not moved in a normal manner, a condition that was more pronounced on the right than on the left side, and that has steadily persisted. The child was unable to sit up until she was nearly a year old, but since then she had developed normally, and is now robust and healthy.

*Examination.* Neither eye can be moved outward, but both eyes can be rotated upward and downward, but not symmetrically. The pupils react promptly to light but not to convergence. Both sides of the face are completely paralyzed. Neither eye can be closed. On attempting to show her teeth there is a slight movement of the muscles of the lower angle of the mouth on either side, this being due entirely to the action of the platysma myoides. She cannot blow out a lighted match held close to her face.

Although the parents declare that this condition was not present at birth, and was first observed when the child was one month old, it seems to me highly probable that the paralysis was congenital, their statement to the contrary notwithstanding.

## REVIEWS.

**THE VITAMINE MANUAL.** A PRESENTATION OF ESSENTIAL DATA ABOUT THE NEW FOOD FACTORS. By WALTER H. EDDY, Associate Professor of Physiological Chemistry in Teachers College, Columbia University. Pp. 121. Baltimore: Williams & Wilkins Company, 1921.

THIS treatise gives a comprehensive, concise account of the present knowledge of vitamin<sup>es</sup>. The discovery of vitamin<sup>es</sup> is described. An account is given of the attempts to determine the chemical nature of vitamin<sup>es</sup> and of the technic for the biological tests to determine the presence of specific vitamin<sup>es</sup>, including the proposed yeast test for vitamin B. The chapter on the sources of vitamin<sup>es</sup> gives, in tabular form, a review of the data on this subject as collected by both British and American investigators. The chemical and physiological properties of the three well recognized vitamin<sup>es</sup> (fat-soluble A, water-soluble B, water-soluble C) are discussed separately. The concluding chapters tell "how to utilize the vitamin<sup>es</sup> in diets," and describe the avitaminoses or deficiency diseases which are produced by lack of vitamin<sup>es</sup> in the diet. Eddy here recognizes beriberi and scurvy as deficiency diseases, and adds "rickets or rachitis seems well on the way to acceptance though the specific vitamin<sup>e</sup> absent in this case is not yet positively identified. Pellagra still resists the efforts of the vitamin<sup>e</sup> hypothesis to bend it to that theory and its etiology is still obscure." A bibliography of 28 pages is appended, covering the literature up to April, 1921; the full title of each cited paper is given. The treatise is intended for both the student and the layman. J. S. H.

**BOWEL DISEASES IN THE TROPICS.** BY SIR LEONARD ROGERS, M.D., etc., London School of Tropical Medicine. Pp. 475; 10 plates; 71 tables and maps. London: Henry Frowde, Hodder & Stoughton, 1921.

ELEVEN and nine years ago, respectively, the author first published books on cholera and the dysenteries. These were reprinted during the war, and are now brought together in a single volume, having been revised and brought up to date, in accordance with the writer's further extensive experience. In addition, a chapter on sprue has been incorporated.

From every point of view, these three diseases are presented in a masterly fashion. A very interesting series of maps has been drawn showing the direction and rapidity of spread of the various cholera epidemics of the last century, from their origin in Bengal, either over the land route through Mesopotamia and Russia to western Europe, or else by the sea route to the Red Sea ports and so to the Mediterranean.

The pathology is very adequately treated, the high points being the colored illustrations of dysentery lesions and the discussion of the pathogenesis of sprue. The author inclines to the view that two organisms play a part in the etiology—a streptococcus of the viridans group (Rogers) and a *Monilia* (Manson-Bahr and Ashford). But it is when we come to the symptomatology and treatment of cholera and amœbic dysentery that we find the most valuable pages. For Rogers is the greatest authority of all time on these two diseases. He will always be remembered as the man who revolutionized the treatment of cholera by introducing the intravenous injections of hypertonic saline solutions, thereby reducing the mortality of the disease from 60 per cent to 33 per cent, and as the first one to make clinical use of emetin injections in amœbic dysentery (1912). It is fascinating to read the reports of his first cases so treated, since they mark two of the brilliant successes in the history of medicine.

M. N.

PRACTICE OF UROLOGY. By CHARLES H. CHETWOOD, F.A.C.S., former Professor of Genito-urinary Surgery, New York Polyclinic. Third edition. Pp. 806; 310 illustrations (7 in color). New York: William. Wood & Company, 1921.

THE third edition of this most worthy text-book has appeared. Standing, as it does, as one of the best rounded expositions of the specialty of urology; better illustrated than any book of its size; thoroughly modern and up to date in every subject, while devoid of many of the older empirical ideas; it may well be recommended to the student—undergraduate and postgraduate alike.

The material is well arranged into brief chapters in their proper sequence and presented in a very readable style with the reasons of the author's opinion, as to the choice between methods of diagnosis or treatment, clearly expressed. Chapter I, on anatomy, contains numerous errors that have persisted since the first edition, such as "Behind, the urethra is connected with the rectum." "The urethra has considerable extensibility, except the meatus, which must be cut," etc., that should have been corrected by now. One misses the exposition of the high-frequency treatment of chancroid, that has rid the clinic of much tedious work; nor can we agree that hexamethylenamin is "especially useful in the alkaline forms of chronic

cystitis," knowing full well that it is inert except in an acid urine. Small errors and oversights such as these mar the value of an otherwise excellent text-book (errors that should disappear in a third edition), and make one hesitate in recommending it without reservations.

A. R.

POLYCYTHEMIA, ERYTHROCYTOSIS AND ERYTHREMIA (VAQUEZ-OSLER DISEASE). By F. PARKES WEBER, M.A., M.D., F.R.C.P. (LONDON). Pp. 148. London: H. K. Lewis & Co., 1921.

THIS timely book by a well-known London authority presents in 60 pages, a revised and expanded form of his critical review of this subject in the *Quarterly Journal of Medicine* for October, 1908. Case reports, notes on the more recent literature and on unpublished cases, together with a good bibliography, make up the rest of the volume. By a curious arrangement the bibliography only includes references not given in full in the text. Parkes Weber draws a sharp and useful distinction between absolute and relative polycythemia, the latter being due to greater concentration of the blood, the former to an increase in the total number of red blood corpuscles in the body. If absolute, polycythemia may be either primary (erythremia) or secondary (erythrocytosis). The latter form is shown in Part 1 to be chiefly due to high altitude or to imperfect oxygenation in congenital or chronic cardiac and pulmonary diseases. In Part 2 primary polycythemia (erythremia, splenomegalic polycythemia rubra, Vaquez-Osler disease, etc.) is presented in the most adequate form known to the reviewer. The author's belief that erythremia is a primary hyperplastic disease of the bone marrow, though open to the objection that it is little more than another way of confessing our ignorance, certainly seems the most logical in the present state of our knowledge. While further studies like those contained in this book may not in the near future be able to demonstrate the cause of erythremia, they should at least greatly reduce the number of cases now being included under this heading.

E. B. K.

ANXIETY HYSTERIA: MODERN VIEWS ON SOME NEUROSES. By C. H. L. RIXON, M.D., M.R.C.S., and D. MATTHEW, M.C., M.B., CH.B. Pp. 120. New York City: Paul B. Hoeber, 1921.

IN 120 pages the authors discuss anxiety hysteria. They recognize three psychoneuroses: (1) anxiety hysteria (including conversion hysteria); (2) neurasthenia and (3) psychasthenia.

In the book only the first is dealt with. By the term anxiety hysteria the authors mean "that condition which is most usually



characterized by a certain anxiety type of facies, headache, insomnia, nightmares and frequently tremor, which symptoms are not dependent upon any organic disease of the central nervous system. It is frequently designated 'neurasthenia' but by the latter term "a condition which is etiologically and pathologically different is herein implied."

Their method of treatment can be summed up in the preface: "While we believe that these psychoneuroses must be met on their own ground and are best dealt with by psychological methods, and while for the most part analytical methods are employed by us, we wish it to be understood that we do not accept all the views propounded by Professor Freud and his followers. We are unable to believe that there is any sexual basis underlying the vast majority of these psychoneuroses, at any rate in military patients; and we hold the view that the emotion of fear is the causal agent at the bottom of ninety-nine out of every hundred such cases. Since, in the minds of the majority of medical men, the term 'psychoanalysis' is inseparably associated with these sexual views, we have altogether eschewed it. In its place we now employ that of 'mental exploration,' a term which is free from those implications, and which was originally devised, on that account we believe, by Professor C. S. Myers. Although we have written what follows mainly with reference to war cases, exactly parallel conditions obtain in civilian patients."

This is one of many books resulting from war experience with so-called shell-shock patients. The only excuse for the book, as stated in the foreword of Dr. A. Lisle Webb, is that it is "written in a way which shall be intelligible to the medical man who has no intimate knowledge of modern psychology and no special experience of psychotherapy."

The method of treatment is essentially psychoanalytic. It is too brief to be of value to the medical man who has no intimate knowledge of the subject and not large enough for the neurologist who wishes to learn more.

T. H. W.

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A MANUAL OF MIDWIFERY FOR STUDENTS AND PRACTITIONERS.  
By HENRY JELLET, B.A., M.D. (DUB.), F.R.C.P.I., L.M., late King's Professor of Midwifery in the School of Physic of Trinity College, Dublin, and DAVID G. MADILL, B.A., M.D., B.CH., B.A.O. (DUB.), L.M., Gynecologist to Monkston Hospital, Dublin. Third edition. Pp. 1168; 20 plates; 570 illustrations. New York: William Wood & Company, 1921.

AFTER a lapse of eleven years this excellent text-book by a former Master of the Rotunda Hospital has been entirely revised and

extensively rewritten. A perusal of the table of contents and the index gives an idea of the completeness of the book which is more than substantiated by a reading of the text. The subject-matter, divided into various sections, deals in a logical manner with the different phases of reproduction, pregnancy, labor, the puerperium, the surgery of obstetrics and the newborn. The section on the toxemias brings out full references to, and discussion of, all recent advances in the treatment of hyperemesis gravidarum, and eclampsia. The authors recommend and practice packing and version for placenta previa, although such other methods of treatment as extra-ovular insertion of rubber bags and Cesarean section for certain selected cases of previas are not condemned. There is an excellent paragraph on pituitrin. The subject of obstetric surgery is gone into fully. One particularly likes the care with which the details of operative procedures are brought out and described. Evidently these Irish authors are conservative in their ideas of obstetric surgery; version for every woman in labor as a time-saving device and the so-called prophylactic forceps operations are not considered in the revision. The volume may be highly recommended as an excellent text on obstetrics.

P. F. W.

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EPHRAIM McDOWELL, "FATHER OF OVARIOTOMY" AND FOUNDER OF ABDOMINAL SURGERY; WITH AN APPENDIX ON JANE CRAWFORD. By AUGUST SCHACHNER, M.D., F.A.C.S., Louisville, Ky. Pp. 331; 21 illustrations. Philadelphia and London: J. B. Lippincott Co., 1921.

THE volume under consideration is a fairly complete exposition of Ephraim McDowell, his life, his surroundings, his confrères and opponents and, of course, his epoch-making work. Of his work the author states: "He placed in the diadem of the art and science of surgery its most brilliant gem and in the eons of time becomes the indirect emancipator of countless millions of human beings from protracted suffering and premature deaths. But after all this priceless service he practically remains unknown and unhonored." The purpose of the book is to acquaint the profession with the difficulties under which he worked and to correct some false impressions concerning him which have been accepted. For example, the traditional story that he was seriously threatened by a mob while performing the operation is based more upon fiction than upon facts. The most interesting part of the book is naturally the part dealing with the first operations, not only from the standpoint of originality, but because it gives the reader a keen insight into surgical practises and equipment of those early days. A section of the book is devoted to Jane Todd Crawford, who played the heroine's part in the memo-

rable "experiment." The author is to be congratulated upon the thoroughness of his work and we presume that the repetitions which have occurred were almost unavoidable. The publishers likewise are to be commended upon the beautiful style in which they have presented the volume. It should be a welcome addition to any medical library.

F. B. B.

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AIDS TO OPERATIVE SURGERY. By H. C. ORRIN, O.B.E., F.R.C.S. Ed., Surgeon, M. of P., Orthopedic Hospital, etc. Pp. 236. New York: William Wood & Company, 1921.

THIS work attempts to present to the student an epitome restricted to the salient features and essential facts of surgical operations. It is not a substitute for the classical text-books, but merely a compend useful to students in preparation for examinations. Each operation is dealt with in the briefest manner possible and only the absolute essentials are given, yet no step has been omitted, each being detailed in the order of its performance in the actual operation itself. Operative technic is not described nor are alternative methods of performing an operation always detailed. Yet the ground covered has been most extensive and the little book bears an important part in a student's library.

E. L. E.

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TEXT-BOOK OF EMBRYOLOGY. By FREDERICK RANDOLPH BAILEY, A.M., M.D., formerly Adjunct Professor of Histology and Embryology, College of Physicians and Surgeons (Medical Department of Columbia University) and ADAM MARION MILLER, A.M., Professor of Anatomy, The Long Island College Hospital. Fourth edition. Pp. 624; 503 illustrations. New York: William Wood & Company, 1921.

THE present revision of this standard text-book has been thorough and includes some changes in the make up of the book. Thus the early processes of development—cleavage, gastrulation and mesoderm formation—are no longer considered separately as such but grouped under the particular animal type, a modification which it is believed will facilitate the presentation of the subject to the student. The second part of the book, on organogenesis, includes a new chapter on fetal membranes and an interesting chapter on teratogenesis. The book is well gotten up, has a very complete index, is copiously illustrated, the photographic reproductions being very good. A good feature of the book is a well-selected bibliography at the end of each chapter. This revision gives a well-balanced description of the developmental processes in the human, and may be well recommended.

P. F. W.

CLINICAL SURGICAL DIAGNOSIS. By F. DE QUERVAIN, Professor of Surgery and Director of the Surgical Clinic at the University of Berne. Third English edition. Translated from the seventh edition by J. SNOWMAN, M. D. Pp. 884; 731 illustrations and 7 plates. New York: William Wood & Company, 1921.

MANY English editions of foreign works in medicine suffer from a lack of adaptability in transposing idiomatic phraseology from one language to the other. The pleasing style and ease in reading of the volume in hand are due to the excellence of the translation, in which the vividness of the author's description suffers no loss.

This third English edition is derived from the seventh original edition. In it there has been added during the revision all new diagnostic points in the surgery of civil practice, and it reflects, also, the many advances in surgery gained by experience in the World War. Over one hundred new illustrations and plates, almost all original and excellent photographic reproductions, have been added. The book follows the former plan, taking up regional surgery, one part after another. Dealing first in the abstract with the morbid conditions of an organ, the author takes up concrete cases in sequence, turning his diagnostic reflections upon them to illustrate a point in question. A characteristic personal note, due to the author's large clinical experience, tinctures the discussion throughout the text. The book is warmly commended as an aid in surgical practice.

P. F. W.

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SURGICAL ANATOMY. By WM. FRANCIS CAMPBELL, A.B., M.D., Surgeon-in-Chief, at Trinity Hospital, Brooklyn, N. Y. Third edition, revised. Pp. 681; 325 original illustrations. Philadelphia: W. B. Saunders Company, 1921.

It is the author's purpose to present anatomical facts in terms of their clinical values. Such a presentation is of distinct value to the student, and should be made use of, as soon as he has become acquainted with any region of the body by dissection. Emphasis is laid upon the normal functions of many of the parts described, and of their deranged functions following accident or disease. Thus in many respects such a book is a physiological anatomy. The author states that only those structures and regions have been emphasized which have a peculiar interest for the surgeon. A glance through the text and index shows how wide his interest is, for practically every organ and region comes up for consideration, with the exception of the pineal body and the coccygeal gland. This completeness is made possible by using short descriptions of structures and by the introduction of many diagrams. Such a commentary on human anatomy must be helpful to all those who are well grounded in the descriptive side of the subject.

W. H. F. A.

COLLECTED PAPERS OF THE MAYO CLINIC, ROCHESTER, MINN.  
Octavo. Pp. 1391; 446 illustrations. Philadelphia and London:  
W. B. Saunders Company.

PAPERS from this clinic need no introduction and no recommendation other than their true title. This collection is especially good and, as usual, contributes a most wide-reaching scope of medical and surgical subjects. The greater number of the authors are writers of widely known reputations and upon whose statements we can depend and place the utmost confidence.

It is useless to single out individual contributions for reference or description. Suffice it to say that the volume holds a most wonderful supply of up-to-date scientific information presented admirably as in the past numbers of this same clinic. E. L. E.

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ESSENTIALS OF LABORATORY DIAGNOSIS; DESIGNED FOR STUDENTS  
AND PRACTITIONERS. BY F. A. FAUGHT, M.D. Seventh edition.  
Pp. 523; 11 full-page plates and 78 text engravings. Philadelphia:  
F. A. Davis Company, 1921.

SEVEN editions of this manual since 1909 are sufficient indication of its popularity with the medical public, and it undoubtedly presents valuable information, especially in the author's chosen field of blood-pressure. Even here, however, one regrets the absence of any consideration of venous pressure, or of Hooker's recent introduction of the capillary blood-pressure into the field of clinical medicine. The section on Clinical Hematology afforded the reviewer the most pleasure, which would have been even greater if a description of reticulocytes and of the resistance of erythrocytes to the usual hemolytic agents had been included. The section on the Sputum is inferior to the more complete original to be found in Bowditch's translation of Sahli's *Diagnostic Methods*. When such extensive adoption of text is made, a different form of acknowledgment would seem preferable. Typographical errors are few; on page 17, the Greek letter  $\rho$  should be replaced by  $\mu$  as a symbol for a micron. E. B. K.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia.**—BARCROFT, BOCK and ROUGHTON (*Heart*, 1921, 9, 7) determined the minute volume of the blood flow in a young man during attacks of paroxysmal tachycardia and during periods of normal cardiac mechanism. The subject was in apparent good health except for recurrent attacks of paroxysmal tachycardia, characterized by sudden onset and offset, shortness of breath, abnormal heart action, cyanosis, gastric disturbance, sweating and weakness. The method of determining the minute volume was that described by Barcroft and Roughton at the meeting of the Physiological Society in July, 1920 (*Jour. Physiol.*, 1920, 15), using the formula:

$$\text{Minute volume} = \frac{O}{A - V}$$

when  $O$  = total oxygen used by the subject per minute,  $A$  = oxygen content of the arterial blood, and  $V$  = oxygen content of the mixed venous blood. With a normal cardiac mechanism and a pulse-rate of 64 the minute volume was 5 liters and the output of the heart per beat, 77.5 cc. During an attack, with a pulse-rate of 198, the minute volume was 2.5 liters and the output of the heart per beat, 12.9 cc. During the attack, also, the oxygen consumption was reduced and the total ventilation, in spite of tachypnea, was diminished. The venous blood showed a high degree of unsaturation; the saturation of the arterial blood, on the other hand, was, if anything, increased.

Paroxysmal tachycardia, then, presents a clear case of anoxemia of the stagnant or ischemic type, which in this case is pushed so far as to cause a reduction in the quantity of oxygen used, *i. e.*, "a crippling of the metabolism."

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**Studies on the Pneumonic Exudate.** V. *The Relation of Pneumonic Lung Protease Activity to Hydrogen Ion Concentration, and a Consideration of the Origin of the Enzyme.*—NYE (*Jour. Exp. Med.*, 1922, 35, 153), continuing the studies that he and LORD have been making on the pneumonic exudate (*Jour. Exp. Med.*, 1921, 34, 199), points out the following facts: As early as 1877 it was demonstrated that leukocytes contain an enzyme or enzymes capable of splitting native proteins to simpler nitrogenous compounds. Opie, in 1906, working experimentally on sterile exudate, showed that there were two distinct proteolytic enzymes present, one derived from the polymorphonuclear leukocytes and acting best in slightly alkaline media, and one derived from mononuclear cells and acting best in slightly acid media. In the early articles it was shown that one enzyme in the pneumonic lung exudate acted best between pH 6.7 and 7.3, and another between 5.2 and 6.3, and the authors formulated the hypothesis that during the course of the disease in the pneumonic lung there is a gradual decrease in pH or increase in acidity. Primarily and at that time when the reaction of the exudate is about that of the circulating blood (pH 7.3 to 7.5) there is a digestion of the more highly organized proteins (fibrin, serum albumen, etc.) following the liberation of enzyme through cellular disintegration. With subsequent increase in acidity (beyond pH 6.7) the activity of this protease diminishes and conditions reach an optimum for the activity of the peptone-splitting enzyme. This peptonase or ereptase carries the splitting of the digestion products to amino-acids, absorbable as such; and resolution takes place. In this study Nye uses fibrin from the blood of horses and cellular suspensions from the consolidated lung. Since normal lung contains some enzyme it was necessary to rule out the action of this. The results show that there is present in the pneumonic lung an enzyme or enzymes capable of digesting horse fibrin which shows the maximum digestion (46 per cent of the fibrin) at pH 8 and the most complete digestion at pH 7. Normal lungs contain an enzyme which is active in a moderately acid medium, pH 4, and essentially inactive in less acid, neutral, and slightly alkaline medium. The possibility of the enzyme coming from pneumococci, cells normally present in lungs, or blood serum, is ruled out. He concludes that the enzyme is derived chiefly from the leukocytes, and is most active in a slightly alkaline medium (pH 8).

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**A Study of the Relation of the Adrenal Glands to Experimentally Produced Hypotension (Shock); with a Note on the Protective Effect of Preliminary Anesthesia.**—RICH (*Bull. Johns Hopkins Hospital*, 1922, 33, 79) found that the observations hitherto published regarding the relation of the adrenal glands to surgical shock were confusing and not infrequently contradictory to each other. The author carried out a series of nicely controlled experiments upon cats, some of which he subjected to adrenalectomy and subsequent intestinal manipulation, and others of which (ten in all) he subjected to identical operative

procedures and manipulation without previous adrenalectomy. Adrenalectomized animals fell into shock precisely as did the normal controls. It was also found that hypotension invariably followed removal of the adrenals before marked indications of asthenia supervened. The experiments prove conclusively that shock is not due to the elaboration of toxic material by the adrenals, since shock occurred equally well in the absence of these glands as in their presence. It seems, therefore, that the only tenable hypothesis by which the adrenals might be linked with shock would be to assume that the operative conditions were such as to completely overwhelm the organism and to render negligible any protective action which the adrenals might exert against shock. The author's conclusion that adrenal dysfunction is not a factor in the production of shock is a difficult one to escape. We should probably not, however, carry the dissociation of adrenals and shock too far. The author has stated that hypotension is one of the essential criteria of shock. He also concludes that the adrenals are a potent factor in the support of normal blood-pressure, since there is invariable hypotension following adrenalectomy. It seems, therefore, fair to conclude that, while adrenal dysfunction does not cause shock in the experiments carried out by the author, yet the fact that adrenal function supports blood-pressure is sufficient to place the adrenals upon the side of those factors that try, however ineffectually at times, to protect the organism from blood-pressure lowering agents.

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**A New Test of Hepatic Function.**—HATIEGAN (*Bull. de l' Acad. de méd.*, 1922, 87, 170), with the aid of the duodenal tube, has studied the elimination of various coloring matters by the liver and regards the indigo-carmin of Voelker as a peculiarly suitable dye for the purpose inasmuch as its appearance is rapid and its elimination of short duration. If injected in doses of 0.16 gm. its excretion is appreciable in about twenty minutes by a grass-green color of bile; this color becomes accentuated and attains its maximum two or three hours after its injection, when its intensity begins to diminish, until after five or six hours it reaches about the same shade which it had attained in the first forty or sixty minutes. In the normal liver, elimination begins after twenty minutes and reaches its maximum in two or three hours. In portal cirrhosis without icterus, 0.16 gm. is not always followed by an appreciable elimination. If the dose, however, is not under 0.24 gm. its elimination may always be made out, but the onset and the rhythm of the elimination are interfered with. In the first hour the bile is unaltered. After an hour the discoloration begins, reaching its maximum in from three to four hours. In five cases of portal cirrhosis without jaundice examined by the writer—cases which resembled one another clinically—the course of the elimination was essentially the same and indicated a delay explicable perhaps by the retardation of the hepatic circulation. The excretion, however, was of the same intensity as normally, but the period of elimination was delayed. A similar delay was observed in a case of cardiac failure. The writer concludes that "indigo-carmin" is eliminated by the normal liver and even by the diseased liver if there be no jaundice. This proceeding may be utilized for the examination of the excretory functions of the liver cell and the permeability of the



bile passages if the cellular excretory function be normal—a circumstance which authorized us in suggesting the employment of this procedure for the examination of hepatic affections in general. The dose necessary for an elimination is 0.16 gm.; to attain the reaction with certainty one must employ a dose of 0.24 gm.

**Observations Relating to the Action of Quinidine Upon the Dog's Heart; with Special Reference to its Action on Clinical Fibrillation of the Auricles.**—LEWIS, DRURY, ILIESCU and WEDD, (*Heart*, 1921, 9, 21), working upon dogs, were able to confirm previous work showing that quinidine causes (1) lowering of the rate of the sinoauricular rhythm; (2) slowing of the auricular-ventricular conduction; (3) slowing of the intraventricular conduction as shown by the increase in the length of the Q. R. S. group. They point out for the first time that conduction in the auricular muscle is also profoundly slowed. In an attempt to analyze the "lowered excitability" which has been noted by many workers, Lewis observed that quinidine in the doses used lengthens the absolute refractory period. Finally, a parietic action on the vagi has been observed. In the light of these known actions of quinidine, the effects of quinidine sulphate upon clinical fibrillation of the auricle are explained, if the last is regarded as fundamentally due to circus movement. "A sufficient lengthening of the refractory period, by reducing the responsive gap, will either bring the circus movement to an end or it will slow the circuit movements. A reduced rate of conduction will slow the circuit movements, but will tend to establish the circus movement more firmly. If the refractory period factor predominates, the circus movement will end; if the conduction factor predominates, the circus movement will not end, but will become slower. An increased rate of ventricular beating under quinidine, in auricular fibrillation, is ascribed to the lowered rate of auricular beating in part, and paresis of the vagi in part."

**Hyperpermeability of the Liver in Diabetes.**—HATIEGAN (*Bull. de l'Acad. de méd.*, 1922, 87, 236) pursuing his studies on the elimination of indigo-carmin by the liver, has observed, in a case of diabetes, a remarkably abundant elimination of this substance, so great indeed that with 0.24 gm. the duodenal content was of a blue color identical with that of the injected solution. The foam even of the duodenal juice was of an intense bluish color, a phenomenon which he had never observed previously. In six cases of diabetes mellitus 0.08 gm. of indigo-carmin—a dose so small that its elimination is not appreciable in the normal liver—was excreted in such quantities as easily to be demonstrable. In one of these cases 0.04 gm. indigo-carmin was excreted in quantities easily recognizable—the elimination following the normal course and rhythm. The writer believes that these observations prove that in diabetes the liver has undergone profound alterations which result in a hyperpermeability in regard to coloring matters. He believes that the hyperpermeability as well as the hyperalbuminosis of the bile suggests that the liver has undergone grave functional alterations and has become a simple "filter." He regards these observations as supporting Glénard's well-known contention that alterations in the liver play a serious role in diabetes. His

cases were apparently all instances of severe diabetes; he refers to them as *diabète consomptif*. Two instances of mild diabetes showed no change. The writer believes that the indigo-carmin test may be of some value as a means of diagnosis between milder and severer forms of diabetes.

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## SURGERY

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UNDER THE CHARGE OF

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**The Results of Ninety-eight Cases of Nerve Suture.**—DARE (*British Med. Jour.*, June 18, 1921, p. 885) says that all his cases are the result of gunshot wounds and have been under observation from twelve to thirty-six months. The author has taken the amount of motor recovery as the standard because it is more important functionally and was more easily determined. Sensory recovery, however, was more complete and earlier than return of motor power. Good or satisfactory results were obtained in 51 per cent of the cases, while 49 per cent were bad results. The series included ulnar, median, musculospiral, sciatic, musculocutaneous and brachial plexus lesions. The only cases to receive any preoperative or postoperative treatment by means of splints were a few of the musculospiral cases. The author feels that 51 per cent greatly exceeds the real truth, especially if one regards recovery from the point of functional usefulness. The results, on the whole, then are in some measure disappointing, considering the tremendous amount of regenerative power that the axis cylinders possess—probably more than any other tissue in the body. The neglect of splints has been responsible for most of the failures, especially with regard to the delicate intrinsic muscles of the hand. Electrical methods have not impressed the author and in the future he will not employ them for it is impossible to know exactly what one is doing in many cases. Moreover, Scheft showed, in 1851 (Langley confirmed his results in 1916), that a denervated muscle is in a state of fibrillation. The keynote of treatment is rest with gradual reëducation to muscles that have been injured by denervation from whatever cause. The recovery of sensation is practically never perfect, but in a great many cases some recovery of sensation returns and this of itself is a great advantage to the individual, protecting him from burns and other injuries and also indirectly leading to an increase of nutritional activity.

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**The Treatment of Syphilis by Intravenous Injections of Mercury.**—LANE (*Lancet*, October 15, 1921, p. 796) says that this treatment was more rapid in its effect than any other method of mercurial adminis-

tration, painless in comparison with intramuscular injections and perfectly safe. One per cent solution of cyanide of mercury was employed and the dosage varied with the tolerance of the patient. It was found that many patients could stand 40 to 50 minims as a dose which was given five times a week. The maximum number of injections was 110 for a very severe frambœsiform syphilide, while the average number ran a little over 40. The strictest attention was paid to hygiene of the mouth and the occurrence of severe gingivitis was rare. Routinely one injection of salvarsan substitute was administered weekly.

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**The Accuracy of the Formalin and Sachs-Georgi Tests for Syphilis.**—KINGSBURY (*Lancet*, October 15, 1921, p. 799) says that the accidental discovery in 1920, by Gate and Papacostas, that the addition of a small quantity of formalin to pooled syphilitic serums produced coagulation, and was without effect on normal serums, forms the basis of this new test. The results obtained from the formalin test prove once again the futility of basing conclusions on figures derived from a small number of cases, as small series have recently been published showing complete accord between formalin and Wassermann reactions. The technic of the test is simple and if the results were reliable it would be an excellent method whereby the practitioner could establish a diagnosis of syphilis. But less than half of the serums giving positive Wassermann reactions showed coagulation with formalin and—a fact of greater importance—nearly 10 per cent of non-syphilitic serums give a positive result. Any claim to the reliability of the test is, therefore, demolished. As early as 1910 it was pointed out that extracts of various organs gave a slight precipitate when added to syphilitic serum. The precipitate was found to be inconstant and was considered to be of little diagnostic value. In 1918 Sachs and Georgi called attention to the fact that the addition of a solution of cholesterol to alcoholic heart extract made a good antigen for a precipitation test. The results obtained are distinctly promising. The technic is much simpler than that of the Wassermann reaction, but there is great difficulty in determining the presence or absence of a precipitate in many instances. A strongly positive Sachs-Georgi reaction may be taken as evidence of syphilis, but a weak reaction must be looked upon with suspicion because of the difficulty in distinguishing between the weakest positive reaction and the slight precipitation given by some negative serums. The detection of the weakest positives may, however, be made easier by modification of the antigen and by special methods of reading the results.

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**The Indications for Surgical Treatment in the Different Types of Goiter.**—SISTRUNK (*Surg., Gyn. and Obstet.*, 1921, 33, 348) says that there are only three types of goiter—colloid, adenomatous and exophthalmic. Other types seen clinically are either variations or combinations of these three. Colloid goiter is definitely a goiter of youth and is the only goiter which disappears under the administration of iodine or thyroxin. The adenomatous type is the most common; 23 per cent of the patients with this type seen in the Mayo Clinic show symptoms of hyperthyroidism, but these symptoms do not develop until

the goiter has been present for an average of sixteen years. In young persons, unless the goiters attain considerable size or produce symptoms of pressure, they are not considered surgical. In the majority of instances after patients with adenomatous goiter have attained the age of twenty-five years surgery is advocated. All goiters of this type associated with hyperthyroidism are considered surgical if the condition of the patient will permit an operation. Exophthalmic goiters occur at any age but most often between the ages of twenty and forty. The condition is best treated surgically and the best results are obtained in patients operated on early in the course of the disease before marked damage has been done to the vital organs. Many patients require one or two ligations of the superior thyroid vessels preliminary to thyroidectomy in order to make it a safer procedure. If care is exercised in selecting the type of operation for a given case the mortality is low.

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**Clinical and Experimental Observations in the Use of Saline Irrigation in the Treatment of Diffuse Peritonitis.**—WILLIS (*Surg., Gyn. and Obstet.*, 1921, 33, 553) says that Murphy and others object to saline irrigation in diffuse peritoneal infection because it tends to produce shock by subjecting the patient to a longer operation, traumatizing the peritoneum and accelerating absorption, while washing off the defensive phagocytes. In favor of free irrigation it may be said that it lessens tendency to shock by prevention of undue loss of body heat. Moreover, it washes out mechanically unabsorbed bacteria, fibrin, pus, blood clots and intestinal contents which may serve as foreign material, facilitating the growth of bacteria. Finally, the peritoneum is an absorbing surface of greatest activity. Ruptured appendix, or appendiceal abscess, is a very frequent cause of fatal peritonitis. The author has had 1034 cases of acute appendicitis in the past twelve years; 33 cases were considered instances of true perforative diffuse peritonitis—some 3 per cent. Fortunately, for purposes of analysis his cases could be divided into two series—the earlier 14 in a period of five years were operated by the principle of rapid operation with minimal abdominal manipulation. The mortality was 50 per cent. The later series was made up of 19 patients, 18 of whom were treated by free incision, the opening of all pockets and combined irrigation with normal saline and the use of a water or electric suction apparatus. The mortality was 16 per cent. The author feels that a shorter and smoother convalescence is gained by this procedure. Of course gastric lavage, opiates and free use of salt solution per rectum and subcutaneously were employed in both series.

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**Further Data Concerning the Experimental Production of Pancreatitis.**—ARCHIBALD and GIBBONS (*Ann. Surg.*, 1921, 70, 426) say that there are three principal theories: (1) The pancreatic lesion is caused by the entrance of bile into the pancreatic duct by reason of an obstruction at the outlet of the common duct; (2) the lesion is caused by an infection travelling from an inflamed gall-bladder to the head of the pancreas by the lymphatic route; (3) that duodenal contents are forced into the common duct through the ampulla, and so into the pancreatic duct. Infected bile aspirated from the inflamed gall-

bladder exercises a much more severe necrosing and inflammatory effect upon the pancreas than does normal bile. Chemical investigation of infected bile has not yet proved that this difference of effect is due to an increase in concentration of the bile salts as the result of bacterial action on the bile. Mild grades of pancreatic swelling as estimated clinically are certainly possible and are represented by edema with early necrosis of the parenchyma, presumably the result of bile invasion. The clinical statement in operation records as to the presence of "a somewhat thickened and indurated pancreas" is probably a correct interpretation of fact in most cases. The gall-bladder, under conditions of irritation from stone or inflammation, is probably able to go into strong muscular contraction and the hypothesis is set up that such contractions may provide sufficient driving force to cause invasion of the pancreas with bile. The common duct sphincter is provoked to resistance not only by the acidity of the duodenal contents but also by sudden distention of the common duct through unexpected rises of pressure in the gall-bladder.

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**Surgical Management of Gastric Ulcers.**—BALFOUR (*Ann. Surg.*, 1921, 74, 449) says infectious foci should be systematically searched for while postoperative direction of diet and habit of living should be included in present surgical management. The selection of operation is of great immediate importance and it is very probable that further progress will come from intelligent selection and application of methods now known rather than from additional operative methods. Four main considerations upon which the value of any operation for gastric ulcer should be judged are simplicity, applicability, immediate results and ultimate results. The author finds in the study of the Mayo Clinic cases that gastroenterostomy with cautery excision of the ulcer surpasses other methods by these standards. Gastro-jejunal ulcer is not wholly a sequel or complication of gastroenterostomy. Ulcers occasionally recur and new ulcers also form sometimes after any type of gastric operation. The author believes that the routine eradication of all septic foci and the adoption of a proper postoperative dietary and therapeutic regimen will be the greatest advance in preventing these recurrences. In the question of protection against cancerous degeneration the problem is unsettled. There is one fact certain—that no operation for gastric ulcer will absolutely assure a patient that he will not die of gastric cancer.

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**Arthroplasty.**—PUTTI (*Jour. Ortho. Surg.*, 1921, 19, 421) says that the modern methods of arthroplasty allow us to create articulations that can attain functional properties which in some cases are equal to those belonging to normal joints. In others the new joint can fully satisfy the most exacting wishes of the patient. These articulations are able to support for many years even the work of trades which are very fatiguing. Some of the author's patients operated on for arthroplasty of the knee and elbow have been declared capable for military service in the late war. In ankylosis of the lower limb it is possible to obtain articulations which are not only quite moveable but also able to support the greatest fatigue. The progress in the field of arthroplasty is due to the interposition method. The author makes free flaps of fascia lata his choice.

## OBSTETRICS

UNDER THE CHARGE OF  
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**Uteroplacental Apoplexy and Accidental Hemorrhage.**—WILLSON (*Surg., Gyn. and Obst.*, January, 1922) reports the case of a patient of unknown history admitted to hospital with albuminuria and edema. The fundus was three fingers' breadth above the umbilicus; the position of the fetus was transverse; the fetal heart was heard in the right lower quadrant and the pelvic measurements were slightly less than the average. Under appropriate treatment the albuminuria disappeared. Labor began with severe pains, and continued for about two hours when bleeding occurred from the vagina with nausea and vomiting. There was great pain and tenderness in the abdomen with prostration. The patient apparently had developed severe shock and considerable bleeding from the vagina. The abdomen was very tender; the uterus tense and hard without relaxation; palpation of the fetus was impossible, but the head was at the brim; the heart could not be heard. On vaginal examination the cervix admitted one finger, and no placental tissue could be found. Diagnosis was made of premature separation of the placenta. At operation there was considerable blood-stained serum in the peritoneal cavity. The uterus was mottled bluish, almost black in color, and the discoloration was greatest in the region of the left cornua. Both anterior and posterior walls of the uterus were involved. There were fissures in the uterine wall, running parallel with its axis. The peritoneum had not been torn through; the tubes and ovaries were apparently normal. On opening the uterus the placenta was on the left side of the anterior uterine wall and one-third separated. The uterus contained over a quart of fluid and clotted blood. The fetus was dead and was removed in its membranes. The uterus was not removed but closed and left, and salt solution was given under the skin. The patient died three hours after operation. At autopsy the liver was pale and softer than usual; the gall-bladder normal; the spleen soft; the stomach and intestines apparently normal. The kidneys were pale and softer than the average; the tubes and ovaries normal, while the uterus showed subperitoneal hemorrhages over its entire surface and in the broad ligament on the side. The wall of the uterus was very soft and the muscle fibers were separated by considerable spaces. There was a central necrosis of the liver lobules, showing slight degeneration and slight fatty degeneration. There was also an acute degeneration in the kidneys and in the muscle of the uterus. There were marked hemorrhagic extravasations between the bundles of muscle fibers. The placenta was apparently normal with the exception of a slight hyaline appearance in the stroma of the villi. The writer has collected reports of 69 cases including his own, and finds that, so far as causa-

tion is concerned, the mechanical theory of distention of the uterus, the forcing of blood into the uterine wall and obstruction to the outflow of the blood from the uterus fail to account for all of the conditions. The weight of opinion tends to the belief that toxemia is the most important factor in causation. There is a striking similarity between the pathological picture, seen in these cases, and the results produced by the toxins of snake poisons. The frequent coincidence of eclampsia and accidental hemorrhage is familiar. Possibly increased blood-pressure, so common in both, may be a factor. The prognosis is always grave, and in 50 cases in which a diagnosis was made during life the mortality was 38 per cent; the fetal mortality was 92.5 per cent in 67 cases. While all cases of accidental hemorrhage are not necessarily fatal and may not require operation, in severe cases occurring before or early in labor immediate operation is demanded. This should always be abdominal Cesarean section. Every effort should be exhausted before the operator proceeds to remove the uterus. If, however, bleeding continues, supravaginal amputation should be done. The Porro operation is often indicated. Uteroplacental apoplexy is caused by the inundation of the uterine wall with a toxin, producing bleeding, liberated from the placenta and naturally producing its greatest effect at the placental site. Accidental hemorrhage in the great majority of cases is a manifestation of the same process. The damaged state of the uterine wall tends to cause both intra-abdominal and postpartum hemorrhage. Where the cervix is undilated and hemorrhage is severe abdominal Cesarean section with hysterectomy is indicated.

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**Treatment of Abortion Complicated by Fever.**—HEBERER (*Zentralbl. f. Gynäk.*, 1921, p. 859) has studied cases of abortion complicated by fever by making a bacteriologic examination of the blood, the contents of the uterus and the placenta. Fifty cases were available for these studies. The results are of decided interest and show how complicated are the findings in bacteriologic cases and how much dependence must be placed on clinical symptoms alone. Within forty-eight hours after the occurrence of the abortion 42 of the patients (84 per cent having fever) were treated by the emptying of the uterus with operative means. These patients made a rapid convalescence without fever and were discharged in good condition in eight or nine days. The interesting part of this paper, which narrates minute and painstaking bacteriologic study, is the statement that one cannot base treatment on the bacteriologic findings in these cases. One must plan his treatment entirely upon the clinical symptoms, including a very thorough and careful bimanual examination. The writer's experience causes him to believe that the best treatment for cases of abortion with fever is to clear out the uterine cavity at the earliest possible moment. HELLEN-DALL (*Zentralbl. f. Gynäk.*, 1921, p. 867) has tried to apply the use of Dakin's solution, as employed by surgeons during the war, to obstetric and gynecologic cases. In 6 cases of abortion complicated by fever, after the uterus had been thoroughly emptied by an injection of from 1 to 3 quarts of 0.5 per cent Dobert's solution there was a rapid fall of temperature. A similar result was obtained in a patient who had parametritis and hemorrhage after an abortion at the fifth month, and when the uterus had been emptied. In this case a midwife had

attempted to extract the placenta. The patient's condition greatly improved and in three days she was practically convalescent. In another case of abortion at three months with retained placenta and very offensive discharge, two quarts of Dobert's solution were used, as an injection followed by the rapid decline of the temperature. There were 6 patients in whom the fetus had died at about the sixth month. In some of these cases the membranes had ruptured and in others they were unruptured; in some the cervix was dilated and in some it was closed. Some had fever without chills and others had chills and fever. These patients were treated with copious irrigation with 0.5 per cent Dobert's solution. In 2 patients the night after the injection was made the temperature rose very considerably and the patient had chills, but after this the temperature fell and the patient improved. In the other cases the use of the remedy was not followed by chills. Perhaps the most interesting result was obtained in the case of a patient who had fever during delivery. The attending physician had stated that the patient required Cesarean section and she had been in labor from four to twenty-four hours. The membranes had ruptured three days previously. A midwife in attendance had examined the patient repeatedly during each day. The attending physician had made an attempt to deliver by forceps. The patient's pulse was 124; her temperature 102.5° F. The os uteri was about two-thirds dilated. The true conjugate was 7.5 cm. and the fetal head was freely movable at the pelvic brim. After a delay of ten hours, during which the patient had pituitrin given three times, the head became fixed in the pelvic brim and the cervix more largely dilated. There was an episiotomy performed and a living child was extracted by the high application of the forceps. The placenta and the amniotic liquid had a very foul odor. After the uterus was emptied it was copiously irrigated with three quarts of Dobert's solution. During the first four days after delivery her temperature reached 102° F.; pulse 120, with very foul discharge from the uterus. After that the symptoms subsided and the patient did well.

## GYNECOLOGY

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**Radiation versus Surgery in the Treatment of Myomata.**—The working rules that have been adopted by CROSSEN (*Jour. Missouri State Med. Assoc.*, 1922, 19, 55) are that radium is the preferable form



of treatment in uncomplicated small and medium-sized myomata in patients in the menopause or near the end of the child-bearing period. Persistent bleeding is usually the serious symptom in these cases and this is promptly controlled by radium, which checks all bleeding, menstrual or otherwise. Nearly all properly selected cases prove amenable to this treatment. It is very important to exclude carcinoma of the endometrium by performing a diagnostic curettage before subjecting the patient to radium treatment. In patients with kidney, heart and other complications giving undue operative risk, radium may be reasonably tried in the somewhat larger growths, especially in those cases where roentgen-ray treatment produces such marked nausea and ill feeling that it is not advisable to continue it. The larger growths in patients presenting undue operative risk are best handled by deep roentgen-ray therapy. In most cases this will, after a time, stop the bleeding temporarily and give a chance to build up the patient for operation. If she cannot be gotten into condition for operation, continuation of the roentgen-ray treatment may stop the bleeding permanently and diminish pressure symptoms by shrinking the growth. If preferred, the smaller growths also may be treated by roentgen-ray instead of radium, with practically the same percentage of symptomatic cures. In over 600 reported cases of myoma treated by roentgen-ray the bleeding was stopped in approximately 95 per cent. However, the roentgen-ray treatment has the disadvantage of extending over a long period of time, or if given in more massive doses in a short period, of upsetting the patient's digestive and nervous systems, in some cases to a serious extent. Large growths, larger than a grapefruit, are best handled by operation. It is not practicable to fix an arbitrary limit of size as other complications have a bearing on the decision. For example, pedunculated subperitoneal growths are not so favorable for radiation as those embedded in the uterine wall and hence must more often be removed by operation. Again, a single large growth is not so favorable for non-operative treatment as a myomatous uterus enlarged to the same size by a number of small nodules. In young women, in whom preservation of the child-bearing function and of menstruation is desirable, myomectomy is the preferable form of treatment, where any serious treatment at all is necessary. In many of these cases the myomata may be removed without disturbing the functions of the uterus. However, a point to be kept in mind is that when the abdomen is opened it may be found necessary to sacrifice the uterus in order to remove the tumors completely, hence myomectomy should be advised only after careful consideration of all the features of the case. If the growths are not of a size and location necessarily interfering with pregnancy or labor, it would be well to try first to check the bleeding by other means, such as curettage and internal medication. If these measures fail, it may be advisable in exceptional cases to employ light doses of radium or roentgen-ray, with the idea of giving just enough to control abnormal bleeding but not enough to affect ovarian or uterine function seriously. But in spite of advances made in the regulation of the dosage and the enthusiastic assumptions of some authorities, the writer regards this as hazardous to the preservation of function and hence employs these measures for this purpose with very decided caution. If the roentgen

ray is used, it is preferable to apply it to one side only, so that one ovary will remain unaffected. In complicated cases, the complications often make operation advisable in a growth which if uncomplicated would be suitable for radium or roentgen-ray treatment. The complication may be inflammation of some adjacent structure, for example, appendicitis or salpingitis. Such associated trouble is found in a considerable proportion of the cases of myoma. It should be remembered that a myoma that begins to grow after the menopause is probably undergoing a degenerative change of some kind and should be promptly removed if the patient is a safe operative risk.

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**Treatment of Inoperable Cervical Cancer.**—Anyone familiar with the subject will realize that there are more cervical cancers that are inoperable when first seen than there are cases suitable for the radical operation. Radium has been of inestimable value in the palliative treatment of the inoperable cases; but unfortunately radium is available to a comparatively small number of the profession, while the inoperable cases of cancer of the cervix are of necessity left to the care of practically all of the general practitioners, many of whom are at a loss to apply any treatment as a palliative. In view of these facts GELLHORN (*Jour. Missouri State Med. Assn.*, 1922, 19, 59) calls attention to a method of treatment which he originated fifteen years ago and which he considers second only to radium in the suppression of the awful symptoms of inoperable cancer of the uterus. The technic is briefly this: The cancerous masses occupying the cervix are scraped or scooped out with a curette, or, better still, with a very large, sharp spoon. This may require a few whiffs of ether or chloroform, but in many cases a preliminary injection of morphine renders this short initial step painless. Do not lose time with attempts at checking the bleeding, which is usually abundant, but raise the foot end of the examining or operating table and insert into the vagina a well-lubricated Ferguson or other tabular speculum. Pour into this speculum a tablespoonful of pure acetone, which will check the bleeding immediately. Lower the speculum after about ten minutes and permit the acetone and clotted blood to run out, and fill the speculum once more with pure acetone. The speculum is now held in place for about fifteen or twenty minutes, usually by the patient herself, after which time the table is lowered so that the fluid will run out of the speculum. The latter is now thoroughly washed out with cotton pledgets soaked in water and then withdrawn. No packing is left in the vagina. There is absolutely no pain connected with the procedure, provided that the acetone does not touch the vulva. Even a single drop of acetone upon the mucosa of the vulva would cause an intense burning, which, however, can be relieved at once by washing it off with water. It is for this reason that a tubular and not a bivalve speculum must be inserted, and that the amount of acetone used must not be so large as to run out and over the vulva. The treatment as outlined above is repeated every two days for at least three weeks, except that the curettage is omitted. Later the intervals between treatments are lengthened to three or four days, and as the condition responds to the applications, treatments are given only as the case requires. The beneficial effect of the treatment is usually very prompt. The hemorrhages are as a rule the

first to disappear. The discharge becomes more watery and soon loses its offensive odor. The general condition of the patient improves fairly rapidly as appetite and strength return, and the severe pain which had interfered with sleep usually decreases to such an extent that very small doses of opiates or even salicylates suffice. Gradually the crater in the vagina shrinks perceptibly and the patient regains, for a time at least, the feeling of good health. The writer has been able to prolong life in this manner with a certain degree of comfort in hundreds of cases, but in spite of such good results he still insists that radium is the best treatment of inoperable cancer of the cervix if it is obtainable, but where not obtainable the acetone treatment is the best substitute.

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**Results of Operations for Uterine Prolapse.**—The results of operations for uterine prolapse, as reported in the literature, after careful follow-up investigation, have been rather disappointing to SPALDING (*Calif. State Jour. Med.*, 1922, 20, 2), so he determined to investigate the results obtained in a series of 76 patients operated upon in the Stanford University School of Medicine. All of the patients in this series had cystocele and 68 had rectocele. The cervix was lacerated in 52 of the patients, eroded in 38 and hypertrophied in 52. The uterus was retroverted in 51 patients, was prolapsed to the vulva in 26, through the vulva in 16, and presented outside the vulva with cystocele and rectocele in 34 patients. The chief complaint with 59 patients was "falling of the womb," although 32 mentioned backache. In all but 1 case some type of perineorrhaphy was done, and in 6 of the more recent cases the rectum was supported by a more extensive proctopexy. In somewhat less than half, the cervix was repaired either by amputation or trachelorrhaphy. 2 patients died from the operation and 13 could not be traced, while of the remaining 61 patients in the series, all but 8, or 87 per cent, were entirely cured of their original complaints. On 19 patients at some subsequent examination, it was possible to demonstrate some degree of recurrence, although many of these patients were relieved of their original complaints. 3 patients had decided prolapse of the uterus. The operations for these patients had not been well planned, inasmuch as the uterus, which re prolapsed after an interposition operation, was pathological and should have been removed, the patient being cured by a subsequent vaginal hysterectomy. In a second case, the interposing the cervix under the bladder after a subtotal vaginal hysterectomy was not successful, the patient later being cured by suspending the prolapsed cervix by laparotomy. Cystocele recurred with 9 patients, but this is an entirely preventable recurrence if the pelvic fascia is overlapped under the bladder. Rectocele recurred in over 22 per cent of the cases no matter what particular type of perineorrhaphy was done. As a result of his investigation the writer concludes that prolapse of the uterus can be cured with a very small degree of operative risk if the patients are carefully observed before operation to exclude other causes for cystitis and backache. Prolapse should recur only rarely after operation and cystocele never, provided infection can be excluded. Rectocele is more difficult to cure unless a high dissection of the posterior plane of the pelvic fascia is made and the rectum fixed to a point behind the cervix.

## OPHTHALMOLOGY

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**Treatment of Choked Disk by Excision of the Sheath of the Optic Nerve.**—KUBIK (*Klin. Monats. f. Augenhk.*, June, 1921, p. 898) sets up the following indications for the treatment of choked disk appearing with symptoms of brain tumor or increased intracranial pressure. (1) All localizable and accessible brain tumors are to be subject to radical operation. (2) In cases of non-localizable brain tumors, including pseudo-tumors, palliative interference upon the skull is to be practised (trephining). (3) Müller's operation of excision of the sheath of the optic nerve is to be practised as the least dangerous operative interference in all cases in which operation upon the brain is refused, and in cases of absence of any special etiology for the occurrence of the involvement of the papilla, when the neurological examination does not indicate a brain tumor; but even in these cases, where the seat of the effect can not be assumed to lie within the posterior portion of the skull, lumbar puncture is the operation of first choice. (4) Where the choked disk does not subside after a palliative operation, or the vision continues to deteriorate, early excision of the sheath should be superadded. In any event, the writer regards this operation as a valuable addition and deserving of extended application. Further experience should lead to greater precision in the indications.

**Genesis of Myopia.**—Probably no question in the entire range of ophthalmology has received greater attention than this of the origin of myopia. The subject is still a live one, as is evidenced by the discussion which is constantly reappearing in the literature. In this connection, HANSEN (*Klin. Monats. f. Augenhk.*, August, September, 1921, p. 171) publishes the results of autopsy of a case of high myopia which, in his opinion, clearly shows the relation between the position of the myopic globe to that of the optic nerve in the orbit. In this case, as is well shown in an accompanying photograph, the enlarged globe was seen to extend backward with the nerve markedly curved in the shape of an S. This case, in his opinion, clearly demonstrates that the nerve not only exercises no traction upon the posterior pole, but that, on the contrary, the bulb exercises a force of compression backward upon the nerve. It may be of interest to give a short *resume* of the hypotheses as to the origin of myopia which assume some sort of traction between the globe and the nerve. Hasner supposed the optic nerve to be absolutely or relatively too short, so that during convergence the nerve caused traction upon the sclera in the region

of the posterior pole. Weiss favored the same view: According to him the free portion of the nerve between the foramen opticum and posterior surface of the sclera is too short. In 1908, Levinsohn emphasized the significance of the position of the head during near work; he assumed that upon bending forward of the head, the eyeball advanced through gravity and venous congestion; the optic nerve, fixed as it is, by connective tissue, bloodvessels and nerves, exercises a not unimportant drag upon the posterior pole and thus occasions the well-known myopic deformation; this writer attempted to establish his hypothesis by experiments upon animals. Finally, Dinger made exhaustive studies upon the influence of the position of the head upon that of the eye, and also of the shape and interior configuration of the same. He agrees with Levinsohn that from the forward sinking of the globe, traction must occur by the relatively shortened nerve; such traction, though slight, he regards as adequate in the developing eye of youth to result in enlargement at the posterior pole and lengthening of the axis.

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**Artificial Eyes.**—COULOMB (*Archiv. d'ophtalmol.*, November, 1921, p. 677) urges the constant wearing of the newer forms of double-shelled prosthesis, as against the former method of wearing the older models (single shells). The latter offer, by means of their posterior concave wall, a lodgment for the tears, forming a veritable moist chamber which macerates the conjunctiva, such maceration causing irritation of the mucous membrane and the mucopurulent secretion, involving the unpleasant necessity of removing the shell during the night and frequently cleansing the orbit. With the double shells there is no space between the bottom of the ocular cavity and the posterior surface of the artificial eye; the tears circulate normally and carry away to the lacrimal drainage apparatus dust and other impurities; no cleansing lotions of any kind are required. To secure perfect tolerance, the shells must be perfect in finish and polish; imperfections hardly supported during waking under frequent winking, become insupportable at night when the lids are closed. The shell should be relatively small and a new one substituted when the first one loses its polish. These shells naturally do not last very long, being worn constantly—eight or ten months on an average. On the other hand, not having to be handled and frequently cleansed, there is little danger of accidental breakage.

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**Difference in Size of the Pupils; Homolateral Miosis from Parasympathetic Repercussion in Affections of the Head.**—LAFON (*Annal. d'oculist.*, October, 1921, p. 736) concludes that unilateral affections of the head, traumatic or otherwise, may occasion an inequality of the pupils, in the form either of homolateral mydriasis or miosis. In the former case, the lesion, in general superficial, provokes an irritation of the centripetal fibers of the thorax lumbar sympathetic system which spreads to the bulbar pupillo-motor nucleus of the same system, resulting in dilatation of the pupil of the same side. In the second case (miosis), the lesion, in general profound, provokes an irritation of the centripetal fibers of the cranial para-sympathetic, or autonomous system, which likewise spreads to the meso-cephalic

pupillo-motor nucleus depending upon the same system, giving rise to a narrowing of the pupil of the same side. Such mydriasis and miosis, from repercussion, are accordingly of the spasmodic type. Beside their homolaterality, they possess characteristics in common of not directly altering the sensory-motor reactions, and of not being accompanied by other elements of the syndromes of excitation or paralysis of the cervical sympathetic or third nerve; such anisocoria becomes more marked in darkness, while it diminishes and tends to disappear in bright light.

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**Ocular Disturbances Complicating Otitis Media.**—GURDIL (*Paris Thesis*, 1921) finds that the ocular complications occurring in the course of otitis media are paralysis of the sixth nerve (9 per cent) and papillary stasis, with or without neuritis, 60 per cent. The paralysis is encountered particularly in those cases of otitis with intracranial complications: The immediate causes are diverse: Foci of circumscribed meningitis, cerebellar abscess, thrombo-phlebitis. Cases have also been observed without intracranial complications; the pathogeny of these is difficult of explanation: In these, too, quite probably there is some affection bearing directly upon the nerve. The alterations of the optic nerve observed in the course of otitis, present themselves under two forms: Simple papillary stasis, unaccompanied by immediate signs of disturbance of function in cases where ventricular hypertension is alone present; stasis with neuritis and rapid failure of vision, when to the ventricular hypertension is added a meningeal infection along the sheath of the optic nerve. Systematic examination of the fundus in the course of otitis media accompanied by general symptoms will alone render possible the detection of such alterations of the optic nerve. Treatment depends upon early diagnosis; good results are obtained in papillary stasis particularly. Lumbar puncture will be of service in cases of slight hypertension; it must be repeated several times. In cases of hypertension with papillary stasis, recourse must be had to decompressive craniectomy; to be effective intervention must be made before the process has proceeded to atrophy. In stasis with neuritis, vaccino-therapy is of prime importance where it has been possible to isolate the infectious germ.

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**Inequality of the Pupils as an Early Sign of Pulmonary Tuberculosis.**—The idea of the frequency of inequality of the pupils in pleuro-pulmonary affections is not a new one; it has been referred to during the past years by numerous writers. SERGENT (*Bull. de l'Acad. de méd.*, April 12, 1921) has made a study of the subject, especially in pleuritis of the apex; he has shown the importance and frequency of unilateral mydriasis from irritation of the sympathetic as a diagnostic mark of early lesions—at times preceding all other signs. The same writer has studied a latent inequality rendered manifest by instillation of a weak solution of atropin 1 : 1000. Before making the test, it is necessary to make sure that the eye itself is free from disease. After instillation, the beginning of the reaction must be observed attentively; it commences in general after ten or twelve minutes, and increases progressively to become complete at the expiration of twenty to twenty-five minutes; one pupil begins to dilate before the

other, increases more rapidly to its maximum, and first loses the light reflex, following which equilibrium between the two pupils is reestablished, both being completely and equally dilated during two or three days. In the reverse order, the healthy pupil returns to its normal condition first, while the other remains larger for a longer time. A detail of great importance is the instillation of the identical quantity of the solution in each eye. The writer sums up the results obtained by the following statistics: 10 cases without pulmonary lesion, test entirely negative; of 18 cases with confirmed unilateral pulmonary lesion, in 11 the pupil test was positive; in 3 cases of absence of pupillary inequality under atropine there was evidence of cicatricial lesions in the chest; in 23 cases with uncertain physical signs, in 15 the test was positive upon the side which had aroused suspicion upon auscultation; in 7 cases with inequality before instillation, the condition became more marked after atropine; in 1 case the inequality was reversed after instillation, but in this case there were bilateral lesions. The above results seem to establish the value of the test; in fact, they are confirmatory of results already obtained by Cantonnet in the same way. It thus appears that the test may render considerable service clinically in affording an additional diagnostic element in doubtful cases.

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**Tuberculous Dacryoadenitis.**—BEAUVIEUX and PESME (*Archiv. d'ophtal.*, January, 1922, p. 22) conclude that tuberculosis of the lacrimal gland is an extremely rare affection. It occurs under two forms: Exceptionally as a caseous process, and more commonly as a sclerosis. It is found in patients with manifest tuberculosis, and again in youths or adults apparently free from all bacillary taint. The disease of the gland is of hematogenous origin, being secondary to some apparent lesion or else to an unrecognized deep focus of infection. The process is an attenuated one, little virulent; it is characterized pathologically by perivascular and periacinous infiltration of inflammatory cells accompanied by typical or atypical giant cells; scleratizing fibrous tissue predominates, forming a barrier to the infection and limiting the same to small circumscribed islets, in the midst of which normal or degenerated acini are visible; Koch's bacillus is almost uniformly absent. Attenuated tuberculosis of the lacrimal gland presents itself in the form of an indurated tumor with slightly irregular surface, mobile, painless, increasing slowly, and capable of spontaneous recession; it may be uni- or bilateral. The prognosis, so far as the local disease is concerned, is favorable; the general prognosis depends upon the degree of systemic tuberculous involvement. The affection may be confounded with benign tumors of the lacrimal gland (adenoma, adenofibroma) and especially with simple sclerotic hypertrophy (chronic dacryoadenitis) which it resembles even to the histological appearances. The diagnosis may be confirmed by inoculation into guinea-pigs. Treatment can be expectant, spontaneous regression being possible: The rational method, however, is extirpation.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**The Endothelium in the Healing of Aseptic Wounds in the Omentum of Rabbits.**—(A continuation of recent interesting experimental investigations of the mononuclear wandering cell of endothelial origin.) FOOT (*Studies on Endothelial Reactions*, v. *Jour. Exper. Med.*, 1921, 34, 625) has resulted in certain important findings which tend to upset our present conception of wound healing. The writer found that in the development of granulation tissue in the omentum in animals "vitally stained" by the use of a carbon suspension, there was active endothelial proliferation resulting in: (1) the formation of new capillaries from the existing capillaries; (2) the formation of vitally stained endothelial phagocytes; (3) the formation of cells bearing carbon granules (thus indicating their endothelial origin), but which also showed fibroglial and collagen fibrils. This third group was somewhat difficult to classify. In all essentials they were fibroblasts, except that they contained particles from the injected carbon suspension. This led the writer into a very attractive hypothesis regarding granulation tissue, namely, that both the endothelium of the vessels and the connective tissue of the part are stimulated in such a way that reversion to an embryonal character occurs. In this state it is apparent that connective tissue cells may be phagocytic for particulate substances, as has been claimed by some, and further, embryonal endothelial cells may even differentiate as fibroblasts under the stress of the need for tissue repair. The writer believes that under these conditions (wound repair) a mesenchyme is formed in which all three types occur, and that they are interchangeable when in the embryonal state. He believes that the endothelium furnishes by far the greater part of the mesenchymal tissue, basing this opinion on actual counts of mitoses in fixed tissue cells as compared to similar counts on vascular endothelium. The formation of collagen fibrils apparently independently of cellular activity is also reported. The writer considers further investigation of Baitsell's work in this line necessary. The nature of the experiments, in which silk sutures were employed, made possible a study of the foreign-body giant cell, or endothelial syncytium, with the interesting findings that both fusion and nuclear division are probably responsible for the formation of these structures. Fusion has been observed and would seem from a study of the origin of the endothelial wandering cell to be the logical process. The writer has further corroborated this view by noting the breaking up into individual cells of syncytia, after the



silk stitch had been completely absorbed. But equally interesting in his finding (in two instances shown in photographs) of mitotic figures in syncytia. The mesothelial layer covering the omentum was never shown to give rise to phagocytes and simply covered the denuded surface, as does the epithelium in skin wounds.

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**Studies on the Nature of the Action of Non-specific Protein in Disease Processes.** I. *Typhoid Protein (Dead Typhoid Bacilli and Soluble Toxin).*—Certain microorganisms, such as the diphtheria and tetanus bacillus, do their damage to body cells by a soluble toxin produced at the local site of infection, while others, such as the typhoid and influenza bacillus and the pneumococcus, wrought their havoc upon liberation of their endotoxin. COWIE and KEMPTON (*Jour. Med. Research*, 1921, 42, 227) conducted a series of experiments as to whether the "sterilizing" changes which occur in the body after an intravenous injection of foreign protein may be explained on purely physical or physicochemical grounds. Guinea-pigs which received intravenous and subcutaneous injections of dead typhoid bacilli (300, 000,000 to a 150-gram pig) showed a definite reaction which was of less severity than that seen in man. It was found that dead typhoid bacilli, after being in contact with diphtheria toxin at 37° C. for one hour, did not form a permanent union with the toxin or alter the toxic effect of the fatal doses of the toxin when introduced along with the toxin, subcutaneously, into guinea-pigs. There was not sufficient absorption or adsorption of the toxin to lessen the effect of the fatal dose when dead typhoid bacilli were allowed to remain in intimate contact with diphtheria toxin at 37° C. for two hours and then separated from the toxin by centrifugalization. Dead typhoid bacilli did not protect against a lethal dose of diphtheria toxin given one week after the last intravenous or subcutaneous injections or near the same time of the injections. Similarly, dead typhoid bacilli, where injected intravenously simultaneously with or on alternate days after the introduction of diphtheria toxin, furnished no protection to guinea-pigs against the toxin.

II. *Horse Serum and Soluble Toxin.*—In a second communication, COWIE and GREENTHAL (*Jour. Med. Research*, 1921, 42, 261) called attention to the fact that 1 cc of normal horse serum, when injected subcutaneously or intravenously into guinea-pigs at the same time as diphtheria toxin, would always protect against a fatal dose or even as high as eight fatal doses, while larger doses of the horse serum protected against larger doses of the diphtheria toxin, although the effect was not necessarily proportional. The highest protection was 15 M.L.D. with 3 cc of horse serum. The protecting power of the horse serum was found to reside in the protein portion rather than the alcoholic soluble fraction.

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**Effect of Blood from Immune Animals upon Transplantable Tumors.**—Many investigators have reported conflicting conclusions concerning the effect of "immune" serum on transplantable tumors in various laboratory animals. KROSS (*Jour. Cancer Research*, 1921, 6, 25) injected, intraperitoneally, one group of Marshall rats with blood

from August rats; a second group of Marshall rats with blood from normal Marshall rats and a third group with no blood. All three groups were then inoculated with grafts of 0.002 gm. of the Flexner rat carcinoma in the right axilla. The same procedure was instituted in the August rat, the immune Marshall rats being used as a source for the immune blood and the Jensen rat sarcoma being inoculated. It was observed that the transfused blood accelerated rather than retarded the development of the tumors as to both time and intensity of growth. The writer states that "if immune bodies do exist in animals that are refractory to tumor growth, they are not resident in the circulating blood." In order to determine whether the blood or other proteins injected acted as a food, a series of rats were injected, intraperitoneally and subcutaneously, with blood, and another series with egg white. One cc of each was administered every three days over a period of six weeks. All animals were then inoculated with the Jensen rat sarcoma. No appreciable difference was noted in the growth of the tumors in the inoculated rats or the controls, the writer believing that the blood did not act as nutriment.

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**An Inquiry into the Distribution of the Blood Groups in Patients Suffering from "Malignant Disease."** — ALEXANDER (*British Jour. Exper. Path.*, 1921, 2, 66) studied the blood groups of 50 patients with "malignant disease," a term including cases of carcinoma, sarcoma, rodent ulcer and leukemia, this last condition being regarded provisionally as a sarcoma of the hemopoietic system. The routine method was to test the patient's corpuscles against known Group II and III sera, a time limit of sixty seconds for the reading being maintained. As controls, the blood group was determined in 50 normal persons and in 125 cases with other diseases, notably tuberculosis, syphilis and tetanus. It was found that, while persons belonging to all four groups are liable to malignant disease, those in Groups I and III appear to be peculiarly susceptible, and the clinical type of disease is, as a rule, more malignant.

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**The Influence of Chaulmoogra Oil on the Tubercle Bacillus.** — Although Walker and Sweeny found that the sodium salts of the total fatty acids of chaulmoogra oil (chaulmoogrates) were highly bactericidal for the tubercle bacillus in vitro, KOLMER, DAVIS and JAGER (*Jour. Infect. Dis.*, 1921, 28, 265) were unable to demonstrate any appreciable germicidal effect in vitro of undiluted chaulmoogra oil and dilutions in paraffin oil on a virulent strain of bovine tubercle bacilli when McMaster's technic was used. In a second series of experiments, it was found that undiluted and diluted chaulmoogra oil exerted no appreciable germicidal influence on *B. tuberculosis* when a vitro-vivo method, utilizing guinea-pigs, was employed. It was also learned that chaulmoogra oil in doses of 0.2 cc per 100 gm. of body weight administered by intramuscular injection at weekly intervals had little or no effect on the course of tuberculosis in infected guinea-pigs. The chaulmoogra oil was relatively nontoxic for the guinea-pigs.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Reinfection in Tuberculosis. Experimental Arrested Tuberculosis and Subsequent Infections.**—"The observant student of the history of tuberculosis will be inclined to reflect that the problems concerning it have a way of recurring." BALDWIN and GARDNER (*Am. Rev. Tuberc.*, 1921, 5, 429) have been studying the question of reinfection in tuberculosis, with special reference to experimental arrested tuberculosis and subsequent infections. These authors state that it seems to them that the frequency of infection is one of the most important of modern problems in tuberculosis, and to it they have devoted their efforts. By frequency of infection is meant the actual number of implantations of tubercle bacilli received into the body from outside sources, not the metastatic spread of a preëxisting focus of tuberculosis; in short, exogenous reinfection as distinguished from endogenous spread by any or all ways, internal or external, but originating in the individual himself. The authors have taken a broad and philosophical view of the situation and summarized their results as follows: In the face of many complexities it is presumption to marshal the known facts into a law applicable to all cases of a disease exhibiting such great contrasts. The medical world seeks for a formula or creates one according to the degree of dogmatism of its author. Then comes a world war and its aftermath of disease and privation; the formula does not apply and confusion reigns again. It is indeed a disquieting thing to contemplate the reported large increase of tuberculosis in Europe and then point to the steady fall in mortality from this disease up to the war years as due to the suppression of the tubercle bacillus. Moreover the abrupt fall of the tuberculosis death-rate in this country since the influenza pandemic has puzzled those who predicted a large increase of tuberculosis following the war and the pandemic. Harmonizing these experiences presupposes more knowledge than we possess, yet not all is mystery. There is a period between the date of infection and the recognition of tuberculosis as a disease that is lost to us in too many cases. The symptoms are absent or too vague and fleeting for our present methods of detection. There are, it is true, the earliest hemoptyses without other symptoms, the definite pleurisies, not to mention the external forms of tuberculosis possible of early discovery. The postmortem not infrequently reveals a group of fairly early tubercles in the lung parenchyma and oftener well-marked tracheobronchial

involvement of uncertain age in individuals dying from other causes. These are not, by any means now at our command, connected with a definite period of time of infection unless we are to except children. There are primary infections, progressive and fatal at all ages. In the races recently brought into contact with tubercle bacilli the matter offers the simple explanation that there is no resting period once the infection had begun to spread. The elements of dosage and frequent cumulative infection must be considered in these cases because of the manner of life of the people. When acute primary tuberculosis is suspected in an adult of the white race and of cleanly habits there has been a tendency to assume an unusual virulence of the bacillus, ignoring the possible absence of resistance from lack of previous infection. Certain families have been devastated by acute tuberculosis where we should expect early infection, and, from the relative immunity thus acquired, a slower course of the disease. It must be remembered that not all the individuals in such families do in fact exhibit such acute forms of the disease, and some, perchance, escape altogether. These again are the puzzling contradictions. To return, therefore, to the main fact of universal infection, single or repeated, for an interpretation of all these variations. It is evident that successive infections do occur and that the first often modifies the course of the later ones. In comparison with the ease with which a primary infection is acquired the later inhaled and ingested bacilli are resisted more or less strongly by the relative "immunity from infection." In applying these principles to human tuberculosis many evidences of confirmation are noted which in the main are satisfactory. There are reasons to suspect mild infection both as to quantity and virulence, occurring infrequently but by a cumulative effect ultimately arousing the disease process. The earliest exogenous reinfections are probably often well resisted and may produce no noticeable symptoms. Good physiological functions combined with the immunity from infection tend to ward off further infection after adult age is reached. Should the conditions be otherwise than favorable, or the infection frequent or potent, disease results. The authors discuss the unlikelihood of massive infections by inhalation and the doubt about other ways of reinfection. From the very small quantities taken in at one time and the slow development of the disease they are inclined to the theory of cumulative infection during childhood and youth. The majority of individuals who are to develop pulmonary tuberculosis for the first time after the age of twenty have already acquired it to a degree. Were it possible to discover these potentially diseased cases who may or may not break down we believe that there would be but a small percentage not accounted for among the victims of tuberculosis in civilized countries. It is virtually impossible to associate many cases of clinical tuberculosis in adults with a recent exogenous source of infection, except under family exposure. Even in family disease, as is well known, the patient often develops the first recognized symptoms years after the death of the relative. Many similar observations might be brought forward to show the futility of trying to place the date of infection, except in those adults (either of primitive races or others) hitherto unexposed because of complete isolation. The town or city dweller is a survivor in the sense that he has reached maturity in the face of more or less inevitable exposure to

human and bovine infection. The result of wholesale physical examinations are impressive in the number of unsuspected pulmonary cases in fair health. What happens to many of these may be surmised from the increased mortality during the war and from the sanatorium records of relapse. Under strain and with an acute influenza, others have come to knowledge but are not yet recorded in the mortality tables. The steady decrease of tuberculosis for years antedating the great war has been variously interpreted, but from the revelations mentioned concerning the large number of undiscovered cases the authors state that the lessening of opportunities for infection has not been accomplished to the extent desired. Yet they are persuaded that the frequency and quantity are lessened. Meanwhile the standards of life had improved, tending to prevent both exogenous and endogenous additions to the already acquired war and its hardships, exposure and starvation. Thousands of arrested or partially arrested tuberculous persons have relapsed and their disease become progressive. Deaths were hastened, and together with influenza the work of years seemed wasted by the war. The amount of disease during the war attributable to reinfection cannot be estimated, but it is safe to say it was but little in the armies. With the crowding of the cities by workers and the combined strain we should frankly expect many new infections. The authors believe that the lesson to be learned and applied is that, hand in hand with efforts to safeguard the young from infection, more attention should be paid to safeguarding both young and old from disease. Without sputum and dairy hygiene the supply of dangerously infected young people will be kept up; without earlier diagnosis, education and favorable conditions of life for the prospective victims clinical tuberculosis will continue at an irreducible minimum.

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**A Work Chair to Prevent Fatigue.**—EMMONS and GOLDTHWAIT (*Jour. Ind. Hygiene*, 1921, 3, 154) illustrate and describe the common faults of seating in workrooms, offices, etc., and present a sturdy chair designed to give support to the small of the back while working at a desk or table and during intervals of relaxation. The chair described is for general use in most occupations in offices and work-rooms. The only adjustment to this chair is different lengths of legs. Especially adjusted chairs may still be necessary for special jobs or special individuals, but the adjustable chair often needs an adjustor. The chair has been successfully tested in an educational institution and in a factory for five years, and is enthusiastically endorsed by the managers.

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All communications should be addressed to—

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ORIGINAL ARTICLES.

THE VALUE OF QUINIDINE IN CASES OF AURICULAR  
FIBRILLATION AND METHODS OF STUDYING THE  
CLINICAL REACTION

FIRST LECTURE.\*

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**Introductory and Historical.** In this lecture and that which follows I propose to deal with the action of certain cinchona alkaloids upon the heart, with special reference to the clinical condition termed fibrillation of the auricle. The alkaloid claiming chief attention will be quinidine, though something will be said of two allied alkaloids, quinine and hydroquinidine.

The first lecture will be devoted to the clinical aspects of the problem; in so far as I shall record original observations I shall record the observations undertaken with my collaborators, Dr. A. M. Wedd, of Pittsburgh, and Dr. C. C. Ilescu, of Bucharest; the second will be devoted more to the experimental and theoretical aspects. This method of description is chosen not only because of its convenience, but also because we owe the remedy quinidine to clinical and not immediately to experimental methods of observation; its original discovery as a remedy for auricular fibrillation has been, so far as I am able to judge from published accounts, one of those happy accidents which at very rare intervals help the progress of medical knowledge. But this statement, if it is not to convey a wrong impression, needs to be qualified. That quinidine would have been discovered as a remedy for fibrillation of the auricles by un-

\* Based on work undertaken for the British Medical Research Council at University College Hospital Medical School, London. A Noble Wiley Jones Lecture delivered at the University of Oregon Medical School, Portland, in May, 1922. Second and third lectures will appear in the July and August issue of this publication.

aided therapeutics is in high degree improbable. The time was ripe for the discovery; it was ripe because irregular action of the heart had been analyzed into its several distinct forms, forms named and recognized the world over.

Consider the frequency with which the human auricle is and has been affected by this disorder fibrillation; consider also the tens of thousands of patients who have received doses of cinchona alkaloids, adequate to produce the change from the disordered to the ordered rhythm, and it becomes inconceivable that this change had not happened many times before Wenckebach specifically drew attention to it. It is the more inconceivable since cinchona has for very many years obtained a vague but quite uncertain reputation as a cardiac tonic.

Given a profession still unable to differentiate between one form of irregularity and another, unable to distinguish between the pulse disordered by fibrillation and the pulse scarcely disturbed by slight changes of respiratory vagal tone, and that profession would have remained ignorant of the profound effects which quinidine exerts upon the heart in a special group of cases. It is when we consider the question historically, and from this aspect, that we are able to grasp, what I think it is important we should at once grasp, that this discovery was made possible only by experiment upon the hearts of lower animals and by the forthcoming analyses of clinical irregularities. The very fact that we owe these remedies primarily to Wenckebach, whose work in this analytical field is for all time classical, speaks for itself. Wenckebach<sup>11</sup> wrote of quinine. In two patients, the subjects of paroxysmal fibrillation, he observed beneficial effects to follow the administration of this alkaloid; it does not appear that Wenckebach gave this drug expecting an action antagonistic to fibrillation. He gave this and many other drugs having very diverse actions; only digitalis bodies and quinine, the latter in a very small proportion of the cases, showed beneficial action. The old and oft-repeated statements that cinchona is of value as a cardiac tonic brought no progress; unaided they could bring no progress. In 1914 Wenckebach discriminated. He named the drug as bringing fibrillation of the auricle to an end.

It was his stated wish for further trials in this specific direction that prompted von Frey's work<sup>7</sup> in 1918. Von Frey used not only quinine, but also its isomer quinidine and other related alkaloids, and from him came the important statement, first, that quinidine is of this series the potent alkaloid, and, second, that it will abort not only short-lasting paroxysms but also long-continued fibrillation. Von Frey's statements were soon confirmed by von Bergmann<sup>4</sup> and by others.<sup>2 3</sup> In the last two years favorable reports have begun to issue from many countries; in America through Levy;<sup>8</sup> in my own country through Drury and Ilescu.<sup>5</sup>

Fully to appreciate this discovery, our conclusions in respect of fibrillation a few years ago are to be remembered. Generally recognized to be the commonest, or the only common grave disorder of the heart beat, it was known to display itself in two forms: in the form of short paroxysms, lasting a few hours or a few days, and much more often as a malady persisting until death. The view was held that if auricular fibrillation had lasted ten days, it was a settled thing. There were, it is true, a few very isolated cases (like that of Lea<sup>s</sup>) where it passed away after lasting a longer time; but the statement still holds that once established for a few weeks, the prospect of its spontaneous passage is beyond reasonable expectation.

Consider briefly its effects: It paralyses the action of the auricles, it wholly abolishes the regularity of the natural pulse, two effects, each of which hampers the circulation in some measure; but it has a third and more malign influence, it lifts the rate of the beating ventricle. The average rate in man at rest is 70 to the minute, in the disordered state the average and uninfluenced rate at rest is about 90 to 100 beats per minute. In quiet walking exercise the normal rate may be 80 or 90 to the minute; in fibrillation the corresponding figures are roughly speaking 130 to 150 to the minute. It is the uncontrolled state of the heart in exercise which constitutes the most serious feature of fibrillation. Thus, fibrillation throws upon the heart a greatly increased burden, a burden which the weakly heart often finds beyond endurance. Because fibrillation of the auricles so upsets the balance between the calls to work and the power to work, because failure with congestion so often follows in its train, it has come rightly to be regarded as one of the outstanding phenomena of cardiovascular maladies. It is upon this condition that quinidine exerts its beneficial action, restoring the normal rhythm to hearts which have beat irregularly for months or years. The drug as now usually administered is given in repeated doses of 0.2 to 0.4 gm. the allowance being from 1 to 2 gms. per diem. The change may come on the first day, it may be delayed for several or many days; but it can be produced in about 50 per cent of all cases so treated. To the question of dosage I shall return in more detail; meanwhile it will be convenient to study the clinical effects more closely; and in doing so I shall first describe methods of observation recently introduced.

**Method of Investigation.** The change from auricular fibrillation to normal rhythm may be recognized by those familiar with the disordered heart action without the aid of instruments; the same event may be recorded graphically by the polygraph. The electrocardiograph, as usually employed, gives further information. It provides a general notion of the events which are happening in the auricle which is coming under the influence of quinidine, events premonitory to the actual change of mechanism. A fall in the rate



of the auricular oscillations and an occasional intermediate phase of "flutter" have been reported by von Frey, who used this method. But electrocardiography as generally employed is not so suitable as a method recently introduced. To study the effects of quinidine upon the fibrillating auricles the oscillations must be recorded in as pure a form as possible; this is not accomplished by leading from the limbs, for the curves are then complicated by fine movements in the corresponding somatic muscles, but by leading directly from the chest wall in the neighborhood of the right auricle, as Drury and Ilescu have shown.<sup>4</sup> This method was first used by Drury and Ilescu<sup>5</sup> in studying the action of quinidine upon the auricle, and has now become the routine practice of my laboratory. By means of this near lead, records can be obtained of the oscillations in a sufficiently pure form to permit of counting, without the introduction of material error. The records give an accurate measure of ventricular rate and its variation, and a sufficiently accurate measure of auricular rate and its change.

The rate of the main auricular oscillations, those which correspond to the circus movements, in clinical fibrillation averages 450 per minute; the actual rates for individual cases are usually near this average rate, but in occasional cases the rate may be as high as 620, or it may be as low as 380 per minute. For any given case the rate of oscillation is remarkably constant over long periods, providing that uniform conditions of observation are maintained. So far as has yet been ascertained, conspicuous alterations of rate are produced only by the administration of certain drugs, though on relatively infrequent occasions there are changes of rate which are imperfectly understood. This constancy of rate under resting conditions has its value to us, for it permits us to obtain clearer pictures and comparisons of changes produced by drugs.

**The Reaction and Dosage.** *Single Doses.* Let us consider first the effects of single doses of quinidine; a dose such as 0.8 gm. of the pure dried base. Such a dose invariably induces a profound reaction, beginning usually half an hour after the drug is swallowed enclosed in a thin gelatine capsule. The auricular rate falls steeply and reaches its minimum usually in two hours after the drug's administration. But this minimum rate is not maintained; very soon recovery begins. This is slow, being spread over twenty-four to thirty hours. Eventually, it is complete, the original rate being reached. Fig. 1 typifies the auricular reaction. Meanwhile, as von Frey noticed, the ventricular rate has been raised; it rises simultaneously with the fall of auricular rate, rises steeply and recovers slowly. The total fall of auricular rate is of 150 or 200 beats per minute, the level reached being in the region of 300 beats or less per minute. The total rise of ventricular rate is variable, in some cases it is comparatively small, in others it is conspicuous and such rates as 140 or even 160 are reached. The recovery from quinidine is due to the drug's elimination by the

kidneys. The alkaloid appears first about two hours after its administration and continues to be excreted for many hours in large quantity; traces may be found twenty-four hours after the administration, but that is not the rule. These statements are based on qualitative tests with Mayer's reagent (mercuric iodide 13.546 gms; potassium iodide 49.8 gms. and a liter of distilled water). In an acid urine, containing the alkaloid, a dense white precipitate is formed by a drop of the reagent. (For further information on the output of cinchona alkaloids see Wiechmann.<sup>12</sup>)

The constancy of these reactions in a given patient may be displayed by repeating them, allowing a sufficient time for recovery to elapse between the doses.

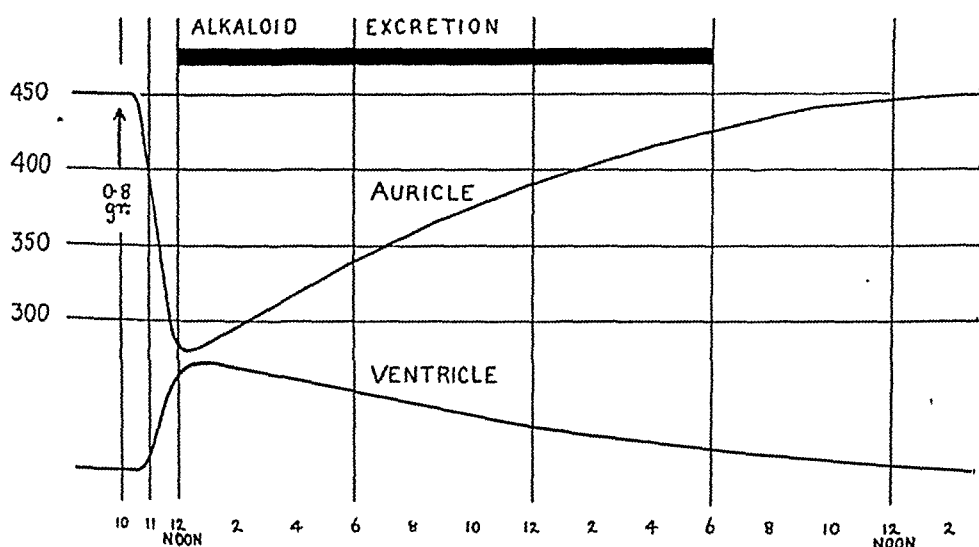


FIG. 1.—A diagram showing the change in auricular and ventricular rates which occurs when a single dose of 0.8 of a gram of quinidine is given by the mouth, in cases of auricular fibrillation. The rates of the auricle are shown to the left; the hours are shown below.

*Increasing Doses.* That the extent of the reaction depends upon the dose is easily proved by the administration of increasing doses at suitable intervals. Thus, if single doses of 0.2, 0.4 and 0.6 gm. are given on alternate days, the falls of auricular rate increase by approximately equal increments (Fig. 2); it is to be observed, however, that 0.4 gm. gives less than double the fall produced by 0.2 gm.; the falls begin from a common baseline, recovery being complete in the intervals between the doses.

*Repeated Doses.* But there is a limit to these regular reactions; an increased dose will not produce indefinitely a correspondingly increased fall. Such at all events seems to be the inference from observations of a slightly different type. If a single dose of 0.6 gm. is given and a second and like dose is administered at such a time that the fall produced by the second dose should begin when the reaction of the first dose is at its height, an equal second fall is not obtained; it is a fall of much less extent.

Similarly, if doses of 0.4 gm. are administered at intervals of three or four hours during the day, the initial fall of rate is rapid and progressive; but there comes a time in many patients when the rate becomes stationary or almost so, falling a little at each dose and rising a little subsequently. To drive the auricular rate lower, an increase in quantity may be necessary, a dosage of, say, 0.6 gm. at four-hour intervals. Even so, stationary rates may be seen. There is a limit to the quantity which may be given safely at single doses, and the failure to obtain further slowing with high dosage is one of the reasons why, in using quinidine therapeutically, treatment has sometimes to be abandoned.

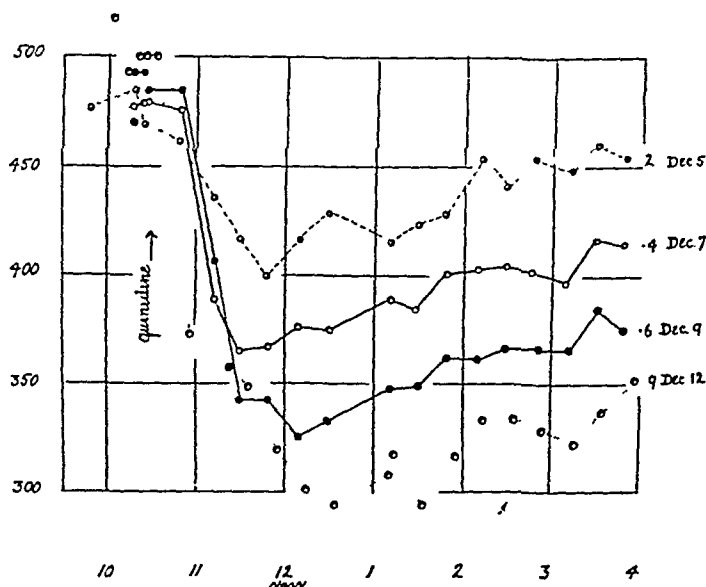


FIG. 2.—Four curves of auricular rate from a case of fibrillation of the auricles, comparing the effects of different doses of quinidine

The desired result, a return of the normal heart rhythm, occurs after very variable quantities of the alkaloid have been administered. In some patients a single dose of 0.6 gm. produces a steep fall which ends in the abrupt cessation of fibrillation. Much more frequently the change is obtained by using repeated doses of 0.4 gm. given every three or four hours each day. The change comes, if it comes at all, usually when the auricular rate falls to such rates as 300 or 250 per minute. In giving repeated doses it is not always necessary to force the rate below such levels; maintenance of the rate at these levels often suffices, the change to normal rhythm coming unexpectedly at any time during the continuance of such treatment. But it is necessary to allow no escape from these rates. The resumption of the natural heart beat does not occur during the phase of recovery from quinidine. Recovery, as we have seen,

occurs with some speed, owing to the quick elimination of the alkaloid; as Drury and Iliescu have pointed out, if three or four doses of 0.4 gm. are given in the day, the rate will fall progressively for that day; but the curves obtained next morning show already that the effects of the drug are rapidly subsiding; the next day's treatment therefore does not start from the last night's level, there is some leeway to make up. To counteract this loss to the reaction one or more similar doses may be given during the late hours of night or early morning. Clearly, the actual doses and times of administration are best controlled by studying the records obtained as treatment proceeds.

It has been said that a single dose of 0.6 gms. of the drug may suffice; in other cases, repeated doses, varying up to total quantities of 10 or 15 gm. may be needed. The precise limits beyond which it is unwise or unprofitable to proceed are still largely unknown.

**Solubility of the Preparations.** Comparisons have been made between salts of quinidine possessing widely different solubilities. We have used test doses of the sulphate, bisulphate, and bihydrochloride, the respective solubilities of which are 1 in 100, 1 in 7 and 1 in 3.6 of cold water. There is no material or constant difference in the time relations or in the extent of the corresponding reactions. When there is any small time difference in the reactions, these do not occur necessarily in the order of solubility. Thus, in the accompanying chart, the bisulphate reaction is most delayed (Fig. 3). The same statement applies to a comparison of the base and its salt. All appear to be rapidly converted into a hydrochloride salt in the stomach, and to be absorbed with essentially the same rapidity. Solubility becomes therefore a question purely for convenience in prescription, where it is desired to give the drugs in fluid form; it is actually our practice to give the drug in thin gelatine capsules.

**Reaction to Allied Alkaloids.** Only two of the allied alkaloids will be discussed at the present time. Quinine, the alkaloid first used by Wenckebach, was reported by von Frey to be less potent than quinidine, and other writers, though not all, have agreed with him. The reason for disagreement probably is twofold: (1) Commercial preparations of the alkaloid often contain very large percentages of impurities and these impurities influence the result; (2) the potency of an alkaloid is gauged by the quantity needed to restore the normal rhythm. Now this quantity varies, not only with different alkaloids but with the same alkaloid, and with the same alkaloid administered to one and the same case. Consequently, comparisons of potency undertaken by the method which has been used are uncertain, and they must remain so unless large numbers of cases are treated alternatively with the two alkaloids to be compared.

There is a quicker method, that which we have recently employed,

namely, the use of fixed test doses and a comparison of the falls of auricular rate. Using this method we find that von Frey's statement is true. Quinidine is weight for weight much more potent than quinine—the fall given by 0.6 or 0.8 gm. of the latter, as compared with that given by quinidine is often inappreciable and rarely amounts to one-fifth of that which follows a similar

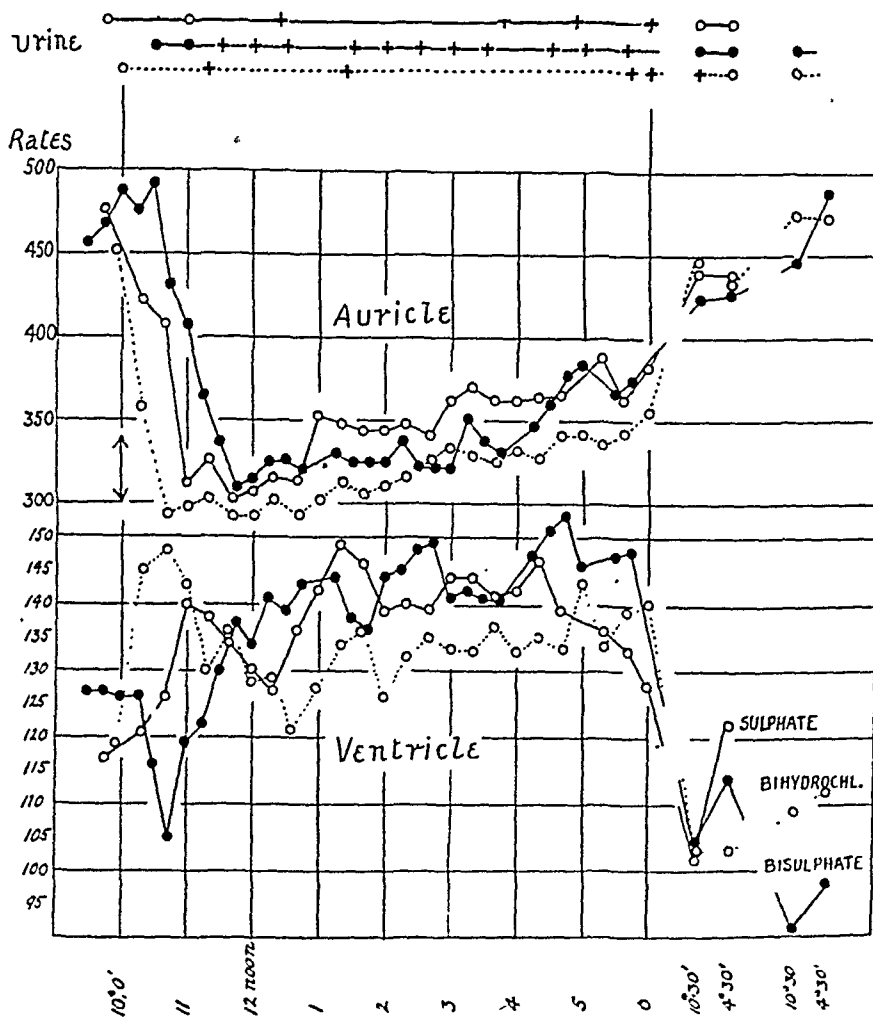


FIG. 3.—Curves of auricular and ventricular rate in a case of auricular fibrillation. The test dose of 0.8 of a gram of quinidine salt was given at 10 o'clock. Above the chart the presence of alkaloid in the urine is indicated by a + sign and its absence by a ° sign. The curves are broken where a night intervenes.

dose of quinidine. The same method of comparison has been used in the case of hydroquinidine; this alkaloid has been tested because it is the chief alkaloid contaminating commercial quinidine preparations; to purify quinidine from hydroquinidine

is not an easy matter and, so I am told, has but recently been accomplished with any considerable measure of success. A comparison of the action of the two alkaloids is therefore a matter of some consequence from the commercial standpoint. Actually, it is found that the two alkaloids have a very similar potency, hydroquinidine being if anything a little the more powerful (Fig. 4).

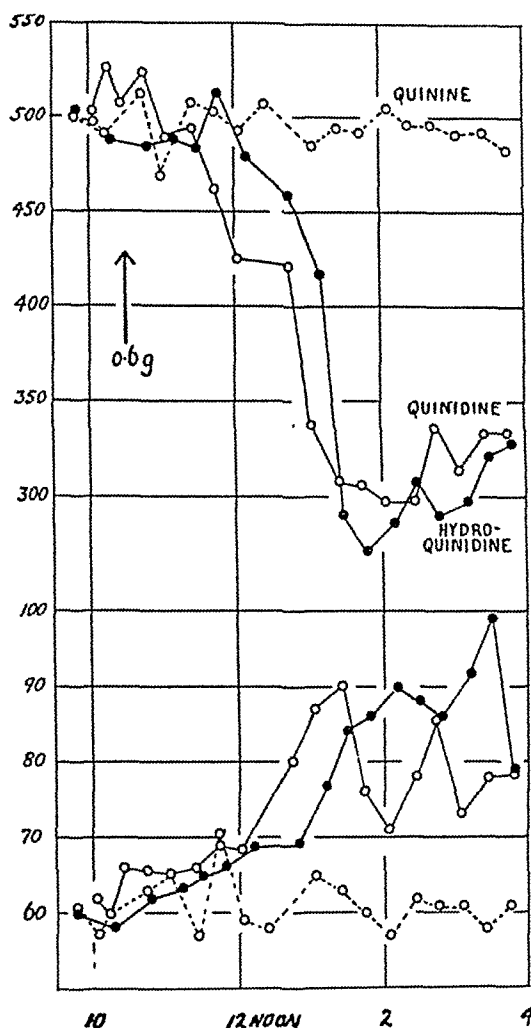


FIG. 4.—A similar chart, comparing the effects of separate test doses (0.6 of a gram) of quinidine, quinine and bihydroquinidine. Auricular curves above and ventricular curves below.

**Simultaneous Digitalis Therapy.** It has been stated on more than one occasion that digitalis interferes with the reaction to quinidine and that the two drugs should not be given simultaneously. Comparisons of the fall of auricular rate obtained by quinidine, before and after the administration of digitalis in full therapeutic doses, usually show but small differences. The original auricular rate is generally speaking a little higher when the heart is under digitalis; the fall in quinidine is usually as great (Fig. 5) or almost as great, though it does not usually reach quite so low a level when digitalis has been given; in some comparisons, too, the fall of rate

has appeared to be delayed by digitalis (Fig. 5); in others a more decided lessening of the fall has been noticed. A striking difference in the two reactions is not the rule; such differences as exist do not seem often to be of consequence, and we think that the antagonistic action of digitalis has been exaggerated. In one patient in whom a change to normal rhythm was repeatedly obtained with a single dose of 0.6 gm. of quinidine (0.4 gm. failing to produce the transition), the same dose was effective after the patient had

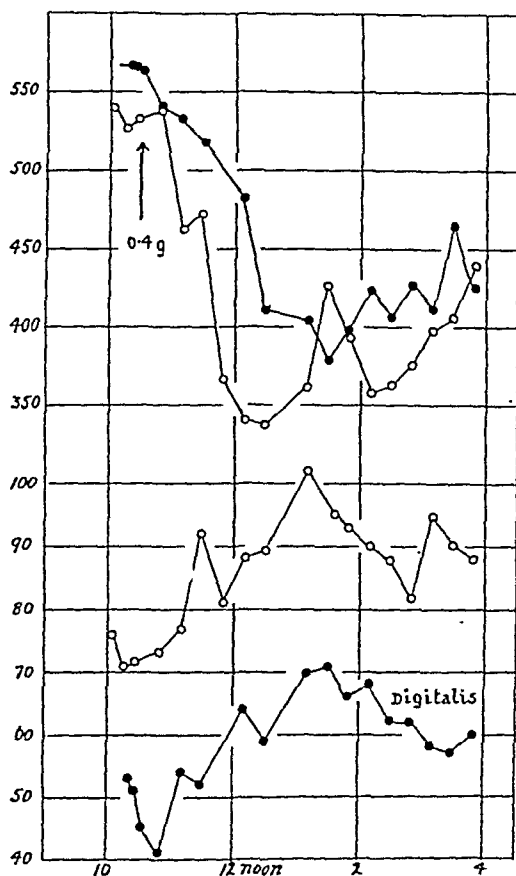


FIG. 5.—A similar chart, comparing the effect of a single test dose (0.4 of a gram) of quinidine, given to a patient before (plain circles) and after (black circles) the administration of nine drams of tincture of digitalis in eleven days.

been fully digitalized. Now the simultaneous administration of digitalis has a great advantage, for it keeps the ventricular rate at a comparatively low level throughout the quinidine reaction (Fig. 5) and one source of trouble is thereby removed. A course of digitalis immediately preceding the use of quinidine, or a lighter course actually simultaneous with the quinidine, seems often to be indicated rather than contraindicated; it may be necessary to

give rather heavier doses of quinidine in these circumstances, but the control of ventricular rate is in many patients a factor of advantage with which we can hardly afford to dispense. At all events the simultaneous administration seems to us to deserve a further and more extended trial in patients predisposed to give high ventricular rates.

**Adverse Effects and Precautionary Measures.** A number of undesired toxic effects have been noted during the administration of quinidine in cardiac cases. Many of these are unimportant. Giddiness, a sense of fulness in the head or actual headache, are not uncommon; gripping pains in the abdomen followed by loose evacuations are apt to occur when large single doses are given. Repeated doses may be followed by urticaria.

**Palpitation.** The ventricular rate rises after quinidine and not uncommonly reaches 120 to 160 per minute; it is part of the reaction and may disturb the patient. A rate of 160 would no doubt on occasion contraindicate the further administration of the drug. That would be the case when the onset of congestion threatened—cases which we regard as in general unsuited to the treatment. In a few cases, if dosage is carried far, the auricular rate may fall toward 200 per minute. When this happens a more serious accident may happen: the auricle is now in a state of relatively pure flutter and the ventricular rate may spring abruptly to the full rate of the auricle (Drury and Ilescu and von Frey). The development of auricular rates below 250 or 240 per minute appears to me to contraindicate further dosage, if the rate of the ventricular rate has already risen much above 100. In cases of this kind, and of high ventricular rates generally, a combination of quinidine and digitalis is preferable.

Under quinidine, extrasystoles arising in the ventricle are frequent. Usually isolated, they sometimes occur in groups, and in a few cases a regular tachycardia may be started in the ventricle. The precise meaning of this interesting phenomenon is not known, but tachycardia of ventricular origin is so closely allied to graver disorders of the ventricle, that the appearance of multiple extrasystoles should be a signal to cease the administration of quinidine.

**Idiosyncrasy to Quinidine.** Some few patients exhibit a serious intolerance of quinidine. Of these I have no personal experience, but von Frey has reported cases in which after a small dose of quinidine sudden loss of consciousness with standstill of respiration has happened. Recovery occurred in his cases, but it is clear from his account that the condition is a very serious one. It is from this experience that the custom has arisen of giving first a small trial dose of 0.2 gm., following this after twenty-four hours by a single dose of 0.4 gm. The treatment is begun on a subsequent day. Whether this method of small trial doses will eliminate danger from this source remains for the future to decide. It is to be remarked that accidents of the kind are rare.



*Dangers of Embolism.* Many years ago I witnessed for the first time a curious and fatal accident. It occurred in a woman suffering from mitral stenosis and heart failure.<sup>10</sup> This woman acquired an attack of fibrillation of the auricles which lasted for several days and then suddenly ended; when it ended clots were detached from the heart, which produced multiple embolism of the lungs and brain, and these led quickly to a fatal termination. Fibrillation of the auricles predisposes to clotting in the auricular appendices. Antemortem thrombi are found in patients dying of heart failure more frequently if the auricles were fibrillating at the time of death. Thus in 76 postmortems on cases dying of chronic heart disease, in which clots were specially sought, I found them in 8 cases out of 23 in which fibrillation was present in the last illness and in only 4 cases out of 53 in which the mechanism had been normal. But embolism due to detachment of these clots does not appear to be more common when fibrillation exists than when the action is normal. While fibrillation predisposes to clotting, the normal auricular action favors the detachment of such clots. In treating patients with quinidine these facts should be born in mind; because we have borne them in mind we have seen no instance in which the resumption of the normal rhythm under quinidine has led to embolism; others have been less fortunate.

When there is much dilatation of the heart, as indicated by congestion of the veins and liver, the therapeutic use of quinidine is contraindicated. In cases in which there have been symptoms or signs of recent embolism, the use of the drug invites disaster. From embolism there is not much to fear providing those chosen for treatment are judiciously selected; but it is to be observed that the peril of embolism precludes the use of quinidine in cases of fibrillation in which the circulation is embarrassed. It sets another limit to its usefulness.

In paroxysmal fibrillation, a fear of embolism should not deter us from giving quinidine. The paroxysm will cease spontaneously after awhile, and clotting is the more likely to occur the longer the attack lasts. Theoretically, if quinidine will bring the attack more speedily to a close, the chances of clotting and subsequent embolism will be diminished.

**The Therapeutic Value of Quinidine.** The percentage of cases in which quinidine, as it is used at the present time, will restore the normal rhythm in the fibrillating auricles is approximately 50 per cent. With these figures, drawn from previous records, the experience of my own clinic agrees. The figure applies to chronic fibrillation of the auricles.

When in a case of auricular fibrillation the normal rhythm is restored, the gain to the patient is considerable. It is not so apparent while the patient lies in bed, for in the cases most suitable for treatment there are few or no symptoms at rest. It is

when the patient goes about again and undertakes his daily duties that he feels real benefit; and the benefit is chiefly due to the heart being once more under strict nervous control. In particular, exercise no longer raises the rate to levels which are incompatible with comfort or which produce actual distress. The change brings similar benefits to the heart as does the lowering of ventricular rate by digitalis; quinidine has the advantage however, in patients in whom its effects are permanent, in that it frees them from further drug treatment. In treatment by digitalis the drug has to be maintained, in most cases indefinitely.

Nevertheless, the usefulness of the drug from the clinical standpoint is limited. It is limited by the high percentage of failures (50 per cent) to restore the normal rhythm. Too much emphasis should not be laid upon these failures however, for it seems probable that the percentage will be reduced as further experience is gathered.

It is limited also by its unsuitability in cases of venous stasis. But the chief limitation is more serious and consists in the early and very frequent resumption of auricular fibrillation. In not a few patients the restored normal rhythm lasts but a few days or a week, and fibrillation returns again and again after successive periods of treatment. In others the normal rhythm is maintained for a few weeks or months; a few cases have been observed in which it has been maintained for six months or a year. In the last group it must be judged an unqualified success, but in proportion as from case to case the return of fibrillation is less delayed, so the remedy becomes less practicable as a remedy. The value of quinidine has so far been greater in adding to our knowledge of fibrillation of the auricles than it has been in therapeutics. It has taught us many important facts, and among the most notable is that the hearts which display chronic auricular fibrillation are *capable* of beating normally, a quality hitherto in doubt. It has also taught us that the cause which predisposes to fibrillation, or at first initiates fibrillation, is maintained in the chronic state. Although it seems clear both from experimental and clinical observation that fibrillation once established tends to maintain itself, it is no longer possible to accept the conclusion that once established it will perpetuate itself indefinitely, though its original cause is removed. The pronounced tendency for the disorder to recur is opposed to any such conclusion; it teaches us that we have still to seek the ultimate causes of the disorder and that the prospect of fully successful treatment is along those lines of investigation.

As in our early publications, my collaborators and myself still deprecate the general use of the drug. At the present stage of investigation it should be employed only under strictly controlled conditions; it is a treatment emphatically for the wards rather than for use in an outpatient department.

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## THE INFLUENCE OF RIGID SALT RESTRICTION IN THE DIET OF CHRONIC NEPHRITIS.<sup>1</sup>

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A YEAR ago Dr. F. M. Allen reported his observations upon the influence of salt restriction in the diet of patients with chronic nephritis and so-called essential vascular hypertension. He stated that the measures usually attempted were ineffective because inadequate, and that rigid chloride restriction, as nearly absolute as possible, would achieve genuine benefits. He reported that following such withdrawal of salt from the dietary he has regularly seen a material fall in the blood-pressure. Among other beneficial effects he also saw improvement in the retinitis and other eye changes of nephritis. I recall his interesting speculation that we may in time come to conclude that sodium chloride is the long-sought-for poison of uremia.

It is generally recognized that the excessive use of salt is harmful, and that its restriction in nephritis is to be recommended; but I have not been able by chloride restriction as ordinarily practised to produce results comparable with those of Allen. Following, then, his suggestion that our restriction of the past has not been sufficiently rigid, I have studied in a small number of hypertension patients over a limited period of time the effect of the almost absolute elimination from the diet of all chlorides. Because the patient frequently complained that this diet produced an intense weakness, it was necessary to limit the length of such observations;

<sup>1</sup> Read before the American Society for Clinical Investigation, Atlantic City, May 9, 1921.

Case No.	Diet.	Blood chemistry.														Urine (24-hr. specimen).				Remarks.
		Systolic blood-pressure. Mm.		Urea N. Mgm.		Creatinin N. Mgm.		Sugar. Per cent.		Chlorides. Mgm.		Chlorides. Gm.		Albu min.		Casts.				
		Begin	End.	Begin.	End.	Begin.	End.	Begin.	End.	Begin.	End.	Begin.	End.	Begin.	End.	Begin.	End.			
1612	15 days, salt-poor 64 days, salt-free	220	205	18.7	8.5	1.00	2.20	0.11	0.17	.692	.493	12.60	1.27	+	++	+	+	+		
2654	62 days, salt-poor 16 days, salt-free	190	165	15.0	10.8 <sup>1</sup>	1.35 <sup>2</sup>	1.87	0.12	0.12 <sup>1</sup>	.499	.504 <sup>1</sup>	16.05	0.89 <sup>1</sup>	+	++	+	+	+		
2693	9 days, salt-poor 18 days, salt-free	250	220	8.9	19.2 <sup>1</sup>	1.10	2.60	0.11	0.10	.491	.453	15.50 <sup>2</sup>	1.30 <sup>1</sup>	+	++	+	+	+	On 63d day. On 9th day.	
3033	51 days, salt-free	200	240	5.6 <sup>1</sup>	14.8	1.50	1.80 <sup>1</sup>	0.11	0.12 <sup>1</sup>	.492	.492	..	..	+	++	+	+	+	On 21st day. On 9th day.	
3048	19 days, salt-poor 38 days, salt-free	218	190	12.4	23.0	0.90	1.64	0.10	0.10	.421	.473	2.79	0.60	+	++	+	+	+	On 14th day.	
3059	15 days, salt-free	180	200	5.3	14.5	1.40	1.55	0.13	0.17	.549	.511	19.80	?	+	++	+	+	+		
3093	13 days, no restriction 10 days, salt-free	198	155 <sup>1</sup>	16.6	18.7 <sup>1</sup>	2.08	1.90	0.11	..	.550	.450 <sup>1</sup>	7.87	1.30	+	++	+	+	+	On 7th day.	
4006	9 days, salt-free	240	270	20.0	30.0	2.70	2.67	0.07	0.09	.481	.506	?	?	+	++	+	+	+	At end of s.-free period.	
H.H.	57 days, salt-poor	215 <sup>1</sup>	172	13.5 <sup>1</sup>	12.8	2.14 <sup>1</sup>	1.42	..	0.13	..	.547	4.48 <sup>1</sup>	4.38	++	++	++	++	++	On 49th day.	

The above table gives data obtained at the beginning and at the end of these observations. The data obtained at various intermediate periods are omitted. "Salt-poor" and "salt-free" periods of diet alternate. Note is made above, however, merely of the total number of "salt-free" and "salt-poor" days.

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and because of the many pitfalls which surround attempts at accurate clinical control of intake and output, the final number of patients upon whom I can report was reduced to ten.

Note was made of the influence of this diet upon the patient's general condition, his blood-pressure, any possible eye changes and certain chemical bodies of his blood. The chloride content of the urine was used as a check upon the accuracy with which the dietary restriction was observed.

Distinction is made in these charts between the salt-poor and the salt-free diets, the latter, of course, being a relative term. With the salt-poor form the patient was given the usual low-calorie nephritis diet with no addition of salt to the food after it reached the table. It is estimated that thus the patient received daily the equivalent of about 2 gms. of sodium chloride. For the salt-free diet the bread and all other foods were cooked without salt and the patient received only such an amount of chlorides as was present in the native foodstuffs. It is estimated that upon this diet the patient received daily the equivalent of less than 1 gm. of sodium chloride. One or two weeks upon the salt-free diet with a variable interim of salt-poor food, and then a second salt-free period, was the rule, although one patient was able to maintain the more rigid diet for a continuous period of sixty-four days.

To summarize: The following results of the salt-free diet were noted.

1. The patient found the food unappetizing and usually ate but little. This factor cannot be disregarded.

2. The blood urea instead of decreasing showed a tendency to increase.

3. The blood chlorides, irrespective of diet, varied but little; while the urine chlorides, reflecting the degree of the patient's adherence to the diet, fell to a very low figure.

4. The systolic pressure, as a rule, showed a moderate fall. This fall was never marked.

5. In two of the patients there developed weakness and prostration to a distressing degree.

6. One of the patients suddenly experienced retinal hemorrhages and other fundus changes at the end of two weeks of this diet.

**Conclusion.** From these limited observations I would conclude that the almost complete elimination of chlorides from the diet of patients with nephritis and vascular hypertension accomplishes little if anything more than does the salt-poor diet ordinarily prescribed.

THE CLOSE RELATIONSHIP OF THE ERYTHROGENETIC  
AND LEUKOGENETIC FUNCTIONS OF THE BONE-  
MARROW IN DISEASE. REPORT OF A CASE  
OF ERYTHREMIA. THE ROENTGEN-RAY  
TREATMENT OF ERYTHREMIA.

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AMONG the cases of erythremia, or polycythemia vera, reported in literature, there are a few cases whose blood pictures have certain of the manifestations of both erythremia and of myelogenous leukemia. The cases have the characteristic symptom-complex of erythremia, (*i. e.*, the polycythemia, cyanosis and enlarged spleen), and in addition they have a definite percentage of myelocytes in the blood. It is a known fact that in certain conditions such as malignant tumors of the bone-marrow and pneumonia in children with a high polymorphonuclear leukocytosis, occasional myelocytes are found in the blood. However, in the case reported and in the cases collected from literature the prolonged presence of myelocytes over a period of two or three years is, we believe, a criterion for assuming that the presence of myelocytes is a leukemic manifestation. We have found five cases on record in which this blood picture is found, and sometimes such cases may be considered as the connecting link between erythremia and myelogenous leukemia or the combination of the two diseases.

That the erythrogenetic and leukogenetic functions of the bone-marrow are closely related is further evidenced by the fact that some of the cases had all of the clinical phenomena of erythremia in the beginning of the disease, and after a period of time presented the clinical picture of myelogenous leukemia, or *vice versa*.

The majority of the cases quoted below present a blood picture similar to our case. The blood picture of the case reported by Hedinus<sup>40</sup> showed a definite polycythemia throughout the course of the disease. The patient also had a myelocytosis, at times being as high as 5 per cent. This patient received roentgen-ray treatment, and after the ninth series the red blood cells increased to 11,540,000. However, on necropsy over a year later

the pathologist reported the case as a typical myelogenous leukemia.

In Rosin's<sup>77</sup> case the interesting feature is that the case was originally diagnosed as polycythemia, and later the blood was that of myelogenous leukemia.

In Winter's<sup>102</sup> case the condition was originally diagnosed as myelogenous leukemia, and later, after establishment of roentgen-ray treatment, changed into what was thought to be polycythemia. This case contrasts with one reported by Rosin in which the opposite state of affairs was true, *i.e.*, the case began as a polycythemia and was later diagnosed as myelogenous leukemia.

In the cases reported by Turk<sup>92</sup> and Nicola<sup>56</sup> a definite polycythemia is present in each case, and occasional myelocytes were found, in Nicola's case up to 1.6 per cent. These cases were included as examples of the comparatively rare cases in which myelocytes were seen along with a polycythemia.

In Blumenthal's<sup>4</sup> case the blood picture is the outstanding example of combination of the two blood pictures, polycythemia and leukemia. (Cases detailed in Appendix.)

In Weber's<sup>104</sup> excellent paper on erythremia he states, "That increased leukoblastic activity nearly always accompanies the increased erythroblastic activity in the bone-marrow is evidenced during life by the usually large number of white corpuscles, especially polymorphonuclears, and by the occasional presence of myelocytes in the circulating blood. At necropsies the examination of the marrow of the shafts of the long bones has shown a decided increase of erythroblastic tissue, and probably in most cases the leukoblastic elements occupy more space in the bone-marrow than the erythroblastic tissues do. These features were greatly exaggerated in Blumenthal's case: the leukoblastic tissues were greatly in excess of erythroblastic. This may be a chain connecting leukemia with erythremia. It is not clear why in erythremia more of the bone-marrow should consist of leukoblastic than of erythroblastic tissue elements. I think the most probable explanation is that in the marrow of such patients (and probably also in that of healthy individuals) the red cells are much more rapidly produced than are the white cells by their respective parents, hence even when the bone-marrow consists chiefly of leukoblastic tissues the red cells far outnumber the white cells in the blood. Moreover, the average life duration of the red cells perhaps exceeds that of the white cells."

Hedinius<sup>40</sup> believes that the irritation which may induce hypererythrocytosis in one person may induce hyperleukocytosis in another. Both red and white cells may be present in the blood in abnormally large proportions, and later one or the other may drop to a very low figure while the count of the other type remains high.

In myelogenous leukemia nucleated red cells are frequently found in the blood; this, too, may be an evidence of increased erythrogenetic activity accompanying increased leukoblastic activity. The condition of a patient suffering from myelogenous leukemia depends a great deal on the red blood picture. As long as the red cell count remains from three to four million the patient continues in a fair condition.

**CASE REPORT.** Male, white, age sixty years; undertaker. Date of admission, December 3, 1917. The history dates back to early in 1916, when the patient applied to his doctor for relief from an attack of hoarseness which had lasted several weeks.

*Family History.* Grandmother died, at the age of eighty years, of old age; mother died at forty-six from postpartum hemorrhage; father died at forty-eight from tuberculosis; one brother died at fifty of heart disease; one sister died of puerperal fever at thirty-six; one sister died at fifty-eight on the operating table, the operation being for a uterine tumor; one brother stillborn at death of mother; one brother living, fifty-seven years of age, and has rheumatism; two sisters living and well.

*Previous Medical History.* Ordinary diseases of childhood except scarlet fever. Patient has had frequent attacks of laryngitis, such as at present time, but nothing serious or incapacitating. He complains of perspiring under the slightest exercise or when the temperature of the air would exceed 65° F. This has existed for twenty years. The patient noted an enlargement under the left ribs, which has increased in size since first noticed. His attention was attracted to this enlargement by the jolting he received from horseback-riding when a boy, the jolting causing him to have pain. Several times he has had pain and aching in the knees and ankles.

*Physical Examination* (made by Dr. J. W. Crumbaugh previous to the present admission). The patient weighed 225 pounds and was 5 feet 9½ inches in height. He was plethoric, hyperemic, florid, lips somewhat bluish, as were the edges of the tongue and pharynx. The uvula was thick and heavy. The postnasal space contained clots of blood mixed with mucus. Teeth showed some pyorrhea. Otherwise the mouth was negative. Neck was negative. Lungs were negative. Heart was negative. Abdomen: An enlarged spleen was found which extended two inches below the pelvic brim and four inches to the right of the umbilicus. The splenic notch was very plainly felt. Extremities negative. Eye examination was negative. Throat examination showed some general thickening of the false chords, a mild form of pachydermia.

After the throat condition cleared up the enlarged spleen was studied. There was no history of malaria, although the patient was born and had lived in a malarial section of the country. His early blood picture had nothing of diagnostic value in it.



Blood count made June 29, 1916, was as follows: Erythrocytes, 5,200,000; leukocytes, 7,200; hemoglobin, 90 per cent.

The differential count showed: Polymorphonuclears and leukocytes, 85+ per cent; small lymphocytes, 7+ per cent; large lymphocytes, 3+ per cent; transitionals, 2+ per cent; eosinophils, 1 per cent; nucleated reds, 3 in 500 cells. Blood-clotting time was five and seven minutes on two occasions. Blood-pressure was 135 systolic and 90 diastolic. Wassermann negative.

The roentgen-ray examination of the stomach and colon after an opaque meal and enema showed that the stomach was pushed upward and to the right; the descending and transverse colon was pushed downward to the right by some mass, probably an enlarged spleen.

The patient did not complain of any feeling of illness for nearly a year. The only complaints were the enlarged spleen, profuse perspiration and prickly heat. The appetite, digestion and elimination were good. In August, 1917, the patient noticed his left leg and thigh began to swell. Posture and a rubber stocking relieved this.

In September, 1917, the patient had the two lower central incisors extracted, after which there was a considerable hemorrhage, very difficult to control, and the white cells showed a definite increase.

October, 9, 1917, in passing a desk, the patient struck his right thigh, which caused a contusion on the upper and outer surface of the thigh. Seventy hours later the right leg, thigh, scrotum and abdomen were ecchymosed and the extremity was enormously swollen, cold and blistered at points. The patient was suffering severe pain. The white cells increased to 49,600. With a decline of the leg symptoms there began a diarrhea of liquid and semi-liquid stools, varying in color from clear water to black, the patient having stools every thirty minutes to an hour, lasting for twenty-four hours. The diarrhea was accompanied by much tenesmus and lower abdominal pain. This lasted to a lesser degree for ten days, and was finally stopped by morphin.

The blood picture remained practically the same until November 19, 1917, (see Table I), when erythrocytes increased to 7,000,000. The patient was now referred for roentgen therapy. The physical examination was practically the same as that recorded above except that the ecchymosis, swelling and pain were less than described above. December 3, 1917, the first day of the roentgen therapy, the following blood count was found: Erythrocytes, 5,810,000; leukocytes, 45,200; hemoglobin, 78 per cent.

The patient was given seven series of roentgen therapy over the spleen and the long bones from December 3, 1917, to April 20, 1920, each series covering the spleen and long bones as outlined by Pancoast,<sup>68</sup> and the results of the blood picture at the end of each series are noted in Table II and III.

TABLE I.—BLOOD COUNTS BEFORE ROENTGEN THERAPY.

Date.	R.b.c.	W.b.c.	Hgb., per cent.	Poly., per cent.	Lym., per cent.	L.m., per cent.	T., Per cent.	E., per cent.	Plat.	Nuc. redds.	Clot. time.	B.p.
June 29, 1916 No material variation	5,200,000	7,200	90	85.0 +	7.0 +	3.0 +	2.0 +	1.0	None	3 in 500	5m-7m	{ 135 90
Aug. 10, 1917	6,070,000	18,000	86	85.2	10, 1917. 6.2	4.8	2.2	1.6	Few	3 in 200	5½m-6m	{ 140 90
Sept. 10, 1917	5,710,000	23,400	100	73.6	23.0	2.4	0.2	0.8	Rare	0	5m-8m	{ 90 130 90
Oct. 9, 1917 Leg Injury.	6,290,000	26,600	104	76.0 +	15.0 +	7.0	0.8	0.2	Rare	2 in 500	5m-6½m	{ 135 90
Oct. 30, 1917	5,560,000	49,600	83	82.0 +	11.0 +	4.0 +	1.0	0.6	Rare	3 in 500	4½m-7m	{ 135 90
Nov. 5, 1917	5,980,000	28,800	81	81.0	12.0	4.0	2.0	1.0	Few	1 in 200	5m-6m	{ 140 90
Nov. 12, 1917	4,750,000	23,400	90	92.6	5.6	1.0	0.6	0.2	Rare	2 in 500	5m-9½m	{ 135 90
Then after one week of iron	7,000,000	9,400	90	73.2	16.8	9.4	0.2	0.4	None	1 in 500	5m	{ 135 90

TABLE II.—BLOOD COUNTS AFTER ROENTGEN THERAPY<sup>1</sup>.

Date.	R.b c <sup>2</sup>	W.b.c.	Hgb., per cent.	Poly., per cent.	Lym., per cent.	L.m., per cent.	T., per cent.	E., per cent.	Nuc. reds.	Myc., per cent.	B., per cent.	Poikil.
Dec. 3, 1917	5,810,000	15,200	78	69.0	10.0	0.0	1.0	0.0	....	2.0		
Dec. 6, 1917	6,210,000	51,800	83	80.0	8.0	1.0	2.0	0.0	....	7.0	2.0	
Dec. 17, 1917	5,520,000	32,300	Dif. Poly.	85-2 nucleated reds.					2.0	2.0		
Dec. 28, 1917	5,850,000	25,800	80	83.0	7.0	4.0	1.0					
Jan. 10, 1918	6,000,000	15,200	85									
Feb. 1, 1918	.....	.....	.....	92.5	3.0	2.0	0.5	....	.	2.0		
April 28, 1918	0,080,000	11,200	100	93.0	6.5	....	0.5					
April 29, 1918	6,110,000	12,100	100	85.5	13.0	....	0.5	0.5	....	0.5		
May 29, 1918	5,900,000	7,300	100	77.0	18.0	....	2.5	0.5	....	2.0		
July 3, 1918	4,990,000	9,800	100	91.0	5.0	....	0.0	0.5	....	0.5		
Aug. 26, 1918	5,500,000	8,000	100	92.0	7.5	....	0.5	0.0	....			
Oct. 25, 1918	5,640,000	21,600	100	97.5	2.5	....	0.0	0.0	....			
Nov. 13, 1918	5,550,000	38,000	100	92.0	5.0	....	0.2	0.0	....	0.5		
Nov. 22, 1918	5,820,000	26,600	100	87.5	6.5	....	5.5	0.0	....			
Dec. 20, 1918	5,870,000	18,900	100	82.0	17.5	....	0.5	0.0	....			
Jan. 31, 1919	5,810,000	15,000	100	81.5	14.5	....	1.0		....			
Feb. 28, 1919	5,460,000	11,700	100	88.5	10.0	10.0	1.0	..	....	0.5		
Dec. 11, 1919	6,950,000	23,000	80	70.0	16.0	10.0	2.0		....	2.0		
Dec. 20, 1919	0,430,000	20,800	90	89.0	5.0	4.0	1.0	1.0	....	1.0		
Feb. 4, 1920	4,200,000	17,600	95	92.0	2.0	3.0	1.0	1.0	....	1.0		
Mar. 22, 1920	5,350,000	12,680	90	83.5	5.5	3.0	1.5	1.0	....	2.5	3.5	
June 8, 1920	5,400,000	6,600	80	92.0	3.0	3.0	1.0	1.0	....			
Aug. 21, 1920	5,100,000	11,100	85	75.0	7.0	17.0	1.0		....			
Sept. 25, 1920	4,200,000	11,000	80	81.0	10.0	6.0	..	1.0	Few	....	2.0	Some.
Nov. 20, 1920	5,800,000	10,200	85	90.0	2.0	7.0	5.0	1.0	Several	....	3.0	Some.
Jan. 21, 1921	0,300,000	23,100	87	75.0	13.0	3.0	2.0	2.0	Several	3.0	2.0	Some.
Feb. 11, 1921	5,190,000	17,400	97	81.0	8.0	4.0	2.0	1.0	Few	2.0	1.0	Some.
Feb. 26, 1921	0,850,000	23,000	97	88.0	8.0	....	1.0	1.0	Occa.	....	1.0	Some.
Mar. 18, 1921	5,690,000	12,000	80	71.0	27.0	....	2.0	1.0		....	1.0	Some.
April 14, 1921	5,160,000	11,800	95	78.0	18.0	1.0		1.0		....	1.0	Some.

<sup>1</sup> Series over long bones by Dr. Ira Burns.<sup>2</sup> The blood counts were done by Dr. Suppington and Dr. V. C. Washburn, of Wilmington, Del., and we are indebted to Dr. J. W. Crumbaugh, Wilmington, Del., for his generosity in furnishing them to us.

TABLE III. DATES BETWEEN WHICH ROENTGEN-RAY EXPOSURES WERE GIVEN.

Series.	Date, beginning.	Date, end.
1 . . . . .	December 3, 1917	December 28, 1917
2 . . . . .	January 11, 1918	March 8, 1918
3 . . . . .	July 7, 1918	July 22, 1918
4 . . . . .	January 14, 1919	February 15, 1919
5 . . . . .	November 3, 1919	April 28, 1919
6 . . . . .	November 20, 1919	January 12, 1920
7 . . . . .	March 8, 1920	April 20, 1920

The patient at present is in good condition and has no objective or subjective symptoms except the enlarged spleen. The last blood count made shows red cells, 5,190,000; white cells, 11,800; hemoglobin, 95 per cent. The differential count shows polymorphonuclear neutrophils, 78 per cent; eosinophils, 1 per cent; large mononuclears, 1 per cent; small mononuclears, 18 per cent; transitionals, 2 per cent; occasional normoblasts and some polychromatophilia.

*Comments.* This patient applied to his doctor for relief of a throat condition, but during the routine examination the enlarged spleen was found, and on being questioned carefully the patient remembered that he had had this mass for years.

The blood count in the beginning was entirely within the normal limits. The differential count, however, revealed a high percentage of polymorphonuclear leukocytes, 85 + per cent, and a low percentage of small and large lymphocytes, 7 + and 3 + per cent respectively; transitionals, 2 per cent; eosinophils, 1 + per cent.

There was no material variation in ten succeeding counts up to August 10, 1917, at which time the red cells increased to 6,070,000 and the white cells to 18,000. The blood counts remained practically at this level until October 9, 1917, when the patient suffered the contusion to his leg, with considerable subcutaneous hemorrhage. At this time the white cells began to increase markedly, and on October 30, 1917, reached 49,600. Following the subsidence of the leg trouble a diarrhea developed coincident with the rise of the red cells to 7,000,000 and the white cells decreased to normal. Later, on December 3, 1917, the red cells decreased to 5,810,000 and the white cells increased to 45,200, with the appearance of 20 per cent of myelocytes in the differential count. It was at this time that roentgen-ray therapy was started.

As to the group under which this case should be classified we are not prepared to say; but if there is a midgroup between erythremia and myelogenous leukemia, or if the two are combined, it does seem that our case should come under this head.

The close union between the leukoblastic and erythroblastic tissues of the bone-marrow makes it difficult to interpret the primary lesion. However, in the case reported above we feel that the

primary disease was that of erythremia, and probably as a result of some unknown influence the excessive demand for leukocytes was too great and myelocytes were produced in abnormally high numbers.

Whether or not this case is a primary polycythemia or leukemia, thus coming under the head of erythremia or myelogenous leukemia, has not been proved, but careful study fails to reveal anything such as Ayerza's disease, syphilis or cardiopulmonary trouble. Lesions such as gumma, tuberculosis of the spleen and thrombosis of the splenic arteries cannot be ruled out, as they can only be ascertained at the autopsy table.

Erythremia<sup>104</sup> is a disease characterized by a well-marked, persistent, relative and absolute polycythemia due to an excessive erythroblastic activity of the bone-marrow, which appears to be the primary morbid factor in the condition and is characterized likewise by persistent increase in the viscosity and total volume of the blood and usually by a cyanotic appearance of the patient and by enlargement of the spleen, for which no local cause, such as obstruction in the splenic and portal veins, is suspected.

Whether or not all cases of polycythemia are secondary to some known or unknown cause is at the present time a debatable question, but we believe, as do many authors, that there is a primary polycythemia or erythremia.

**Pathology of Erythremia.** In almost every case of erythremia that has been systematically studied at autopsy there is evidence of increased erythroblastic activity of the bone-marrow. Where the bone-marrow in the shafts of the bones in adult life is normally of the yellow or fatty kind, most of it has been replaced by red bone-marrow, thus increasing to a considerable extent the erythroblastic activity. Along with the increase in the erythroblastic activity there is usually an increase in the leukoblastic activity, and in some cases, such as those of Hedinus,<sup>40</sup> Blumenthal<sup>4</sup> and others, the leukoblastic tissues are in excess of the erythroblastic tissues and make one suspect a leukemia rather than an erythremia. The fact that there is an increase in the erythroblastic and leukoblastic activity may be recognized during life, *i. e.*, the increase in the cells of the blood and the occasional finding of erythroblasts and myelocytes in the circulating blood. In one case<sup>104</sup> in which a biopsy was performed the bone-marrow was found to be in a state of increased erythroblastic activity.

The splenic enlargement which is found in most cases seems to be due to a hyperplasia of the splenic pulp and the connective-tissue elements and an engorgement of the spleen by blood, the spleen acting as a reservoir. There are other cases in which the enlargements have been explained by the finding of thrombotic infarcts, tuberculous nodules or gummas. At any rate the enlargement is believed by a number of authors to be a compensatory process.

The great majority of pathologists now consider leukemia to be a primary morbid disease of the bone-marrow, no matter whether the condition is of the lymphatic or myelogenous variety. The secondary enlargements of the glands is thought by many to be due to a metastatic deposit of myeloid elements with subsequent proliferation *in loco*. Stengel<sup>82</sup> is of the opinion that leukemia is akin to some of the sarcomata.

It would certainly seem, from a pathologic standpoint, that erythremia and myelogenous leukemia are closely related, and in some cases we may find evidence of an involvement of both the erythroblastic and leukoblastic tissues of the bone-marrow. In the five cases reported there is a definite myelocytosis present along with the polycythemia, and these cases have been termed polycythemia because of the increased red cell count, and in at least two of the cases the pathologist returned a diagnosis of leukemia. Both erythremia and leukemia have their origin in the bone-marrow, mattering not whether they are primary or secondary to some known or unknown cause. They both cause enlargement of the spleen, and ultimately both are fatal.

Roentgen and radium therapy certainly have played the major part in the treatment of leukemia; in some cases the lives of patients have been prolonged for many years. In leukemia we have treated the bone-marrow of all the long bones and the spleen, giving inhibitive doses over the bones and destructive doses over the spleen. Now if erythremia is closely related to leukemia, that is, affecting the erythroblastic tissues instead of the leukoblastic, we feel that roentgen therapy should be given a careful trial in the treatment of the condition. As in leukemia, all symptomatic treatment of erythremia has failed to give any but temporary results, we therefore propose and recommend roentgen-ray therapy, giving inhibitive doses to the long bones, with the view of inhibiting the formation of red cells, and stimulating doses over the spleen with the view of increasing the normal function of the spleen.

**Treatment** In a preliminary paper<sup>65</sup> the roentgen-ray treatment over the long bones and spleen in erythremia was recommended. Since writing that article it has been gratifying to see from the literature that a few other roentgenologists<sup>5 24</sup> had or have been following out practically the same method of treatment as advocated by us, and with good results.

The experiments of Heineke, Linser and Helber, Tatarsky, Fränkel and Budde, Aubertin and Beaujard and Price-Jones<sup>16</sup> have shown us that the roentgen-rays have a decided effect upon the blood and spleen. Although some of the experimental data as to the mechanism of the changes produced differs with different experimenters there is more or less unanimity of opinion as to the outcome of the results:

1. The spleen is more sensitive to the roentgen-rays than the bone-marrow.

2. After moderate doses of the roentgen-rays the leukocytes show an initial rise followed by a pronounced fall and subsequently rise to normal.

3. The red cells show an initial fall after moderate doses of the roentgen-rays. This may last for long periods of time or the cells may rise to normal in the course of a few days.

As to the ultimate success of the roentgen therapy of erythremia one must wait and see the results of the treatment of various cases and the observation of such cases over a number of years. However, roentgen-ray treatment is only an agent recommended in an effort to find something that will give relief to this class of patients where drugs are of no avail, and venesection, etc., only of initial improvement, the patient relapsing into the primary state in a comparatively short time.

If we accept the views of a number of pathologists and assume that the disease is one primarily of the bone-marrow, and the lesion is a primary hyperplasia of the erythroblastic tissues, our treatment should be that of the bone-marrow, with the view of inhibiting the excessive formation of red cells; or if all cases of erythremia are secondary to some exciting cause foreign to the bone-marrow, as considered by some, roentgen-ray therapy is recommended in those cases in which no primary cause can be found and have failed to respond to the usual method of treatment.

The treatment of the spleen is given with the view of stimulating the functions of that organ. There is some histologic evidence<sup>63</sup> that the spleen destroys erythrocytes by the phagocytic action of the cells of the spleen. The spleen is very susceptible to the action of the roentgen-rays, hence we must make the exposure a stimulative one. There is no experimental evidence to support the assumption that stimulative doses of roentgen therapy over the spleen increase the hemolytic action of this organ, although Fränkel, Budde, Fionne and Zironi<sup>16</sup> have worked on this particular subject. However, we feel that theoretically the functions should be increased and are therefore working on that basis.

The details of the technic are very similar to the treatment followed out in the treatment of leukemia recommended by Stengel and Pancoast,<sup>82</sup> and have been outlined in a previous paper. The technic and dosage have been reached by experience and results in other cases. We recommend that a complete blood count be made at least once a week during the treatment, keeping in mind the white cell count particularly, as it is very important that the white cells be kept as near normal limits as possible, and by this prevent the elimination of one of the body's defences against infection. White cells are more easily destroyed than reds, and the blood counts are our only index to the possible immediate results of the treatment. If in the blood counts the total white cell count goes below 4000 treatment should be discontinued for a time until

it becomes normal, and in the differential count if the polymorphonuclears decrease to 35 per cent, treatment should be discontinued until the percentage of the polymorphonuclear leukocytes increases.

1. The radiation is made primarily over the bones of the entire skeleton except the bones of the head, these being omitted, due to the likelihood of the loss of the hair in this region. The bones are mapped into areas so that all of the bones can be covered. The size of each area depends upon the diaphragm opening in the tube and the skin target distance. Our areas are usually about twelve inches long over the long bones, protecting at the same time the other parts of the body with lead and lead rubber, thus preventing overlapping of exposures.

2. Each area is exposed regularly and systematically, and it is recommended that the maximum dose be distributed over three successive days rather than at one time. This prevents a too rapid reduction of the blood cells.

3. Exactness in dosage is essential. We give somewhat less than the erythema dose, as we do not wish to destroy the bone-marrow but to inhibit its function. Our dosage is calculated according to the inverse square of distance, and we use 5mm. aluminum filter, spark gap of nine inches, milliamperage of five and skin target distance of eighteen inches.

4. Frequency. Daily exposures are advocated until the series is completed, and in erythremia two areas are exposed daily. After the body has been covered once we allow an interval of ten days to elapse and then give another series over the bones, giving two such series before treating the spleen, provided the white cell count is not too low.

5. Direct exposure of the spleen is given after the bones of the skeleton have been covered twice, and at this time we give one-half an erythema dose with the expectation that it will have a stimulative effect on the spleen.

6. Duration of the treatment depends upon the individual patient, the blood count being an index as to treatment. Our goal is to bring the blood picture as near normal as possible and as quickly as it can be safely carried out, taking care that too long intervals do not intervene between series.

The patient reported in the case history above received the following treatment: Roentgen-ray treatment was given. There were seven series given over the bones and spleen, and in addition at times cross-firing applications were given over the spleen because of the presence of myelocytes complicating the polycythemia. The dates between which roentgen exposures were given can be seen in Table III. In the treatment of this case daily exposures were not always given, due to the inability of the patient to come in for treatment.



The blood counts after the beginning of the roentgen-ray treatment showed a gradual decrease in the white cell counts and a marked decrease in the percentage of myelocytes. The red cell counts ranged between 4,990,000 and 6,240,000 until August 26, 1918, when they increased to 9,500,000. We cannot explain this rise unless it is possibly due to a too rapid destruction of splenic tissue and by this decreasing or eliminating the normal functions of the spleen. Similar rises in the red cell counts were noted by Winter<sup>102</sup> and Hedinius<sup>40</sup>—in Winter's case to 7,000,000 and Hedinius's case to 11,540,000. Dr. Simon, the roentgenologist who treated the case reported by Hedinius, in a personal letter to me states: "My cases were all treated through only 1½ mm. aluminum and with a dose that now must be considered too small to act sufficiently through the thick cortex of the long bones. Perhaps these doses could be even dangerous acting as irritating doses."

Roentgen-ray therapy in our case was started again on January 14, 1919, and the red and white cell counts have gradually decreased to a point within normal limits with a disappearance of the myelocytes from the blood stream.

After the seventh series of the treatment the patient's blood count was practically normal and remained so until January 24, 1921, at which time he was given a series of exposures over the long bones only. His blood count at present is within normal limits and the patient feels fine.\* He has no cyanosis or florid color, but he does possess an enlarged spleen. A singular fact in the treatment of this case was that the spleen increased in size, *i.e.*, it is larger today than when first seen in spite of the occasional cross-fire radiation by the roentgen-ray.

**Conclusions.** 1. Erythremia is a disease of the erythroblastic tissues of the bone-marrow.

2. Roentgen-rays destroy or inhibit the formation of red cells.

3. Roentgen-rays should be used in the treatment of erythremia.

4. Roentgen-rays should be used in the treatment of secondary polycythemia when such cases fail to respond to other treatment such as drugs, venesection, etc.

5. Roentgen-ray treatment has been efficacious in the case reported above, and it has proved of value in cases reported by other roentgenologists.

6. Roentgen therapy effects a more permanent result than any other therapeutic measure used or recommended up to the present time.

**Appendix.** CASE OF HEDINIUS.<sup>40</sup> Female, single, age sixty-five years, under observation for two years and ten months, from February 5, 1912, to November 20, 1914. Typhoid fever at fifteen

\* A more recent blood examination shows that the patient has an anemia: Red blood cells 3,000,000; white blood cells within normal limits; hemoglobin, 65 per cent. Count made October 26, 1921.

years of age. Menopause at forty. Luetic history negative. In 1906 she had ulcer ventriculi. In 1907, the patient has a molar extracted, after which she had a hemorrhage. At the same time the patient noticed a tumor in the left hypochondrium and began to suffer from headache, dizziness and cyanosis. In 1908 she suffered from pulmonary tuberculosis. *Physical Examination* February 5, 1912. Patient slender; weighs fifty kg.; temperature subnormal; skin of face, neck and thorax red and a profuse perspiration was localized to this area. Heart negative except accentuated aortic sound. Lungs showed signs of chronic tuberculosis at one apex. Urine: albumin, 2 per cent; some red cells and cylindroids were found on microscopic examination. Thyroid normal. Liver enlarged, edge soft and palpable. Spleen enlarged, extending beyond a little over the midline and down to the crest of the ilium. The tibia and the sternum were tender to percussion.

	Erythrocytes.	Leukocytes.	Hemoglobin.
February 1912 . . .	6,500,000	42,000	per cent.
October 26 . . . .	11,540,000	..	109
1913 . . . . .	5,980,000	29,800	95
1914 . . . . .	6,440,000	11,280	96

All of these counts were made at the same time of day.  
The differential leukocyte examination was as follows:

	1912. per cent.	1913. per cent.	1914. per cent.
Polymorphonuclears . . . . .	79.0	81.0	77
Eosinophils . . . . .	1.0	5.0	8
Basophils . . . . .	1.0	1.5	2
Small lymphocytes . . . . .	2.5	3.0	6
Mononuclears . . . . .	11.5	4.0	3
Myelocytes . . . . .	5.0	3.0	1
Large lymphocytes . . . . .	..	2.5	3

Viscosity, May 7, 1913, 10.48 mil. Hemolysis, November 1, 1914, 0.3 to 0.4 per cent NaCl before hemorrhage.

Roentgen-ray treatment of the spleen and long bones began in February and the patient received nine treatments and the white cells decreased from 42,000 to 21,800 by October. After the fourth treatment with the roentgen-ray the white cells increased to 124,800 and later went to 10,000 after the eighth or ninth radiation. The red cells were 6,500,000 before the roentgen-ray treatment and went up to 11,540,000 after the ninth roentgen-ray treatment. Roentgen-ray treatment stopped and the red cells decreased to 6,000,000.

Benzol, 1.5 gm. per day, was tried for twelve days. The red cells increased from 6,000,000 to 10,200,000 and the whites increased from 29,800 to 54,600.

After spring, 1913, the patient's condition was unchanged for a year until the summer of 1914, when it changed for the worse. The

liver and spleen increased very markedly in size. Tubercle bacilli could not be found in the sputum. The albumin in the urine increased to 4.5 per cent. Ascites developed.

Blood-pressure in 1913 systolic, 160 to 170: Blood-pressure in 1914: systolic, 127.

The patient died November 30, 1914.

*Necropsy Findings* (by S. Hesser and Sven Lindblom). Skin pale. Poor musculature development. Abdomen swollen. Inguinal glands enlarged. Liver and spleen enlarged. Heart negative. The lungs showed one area suspicious of tuberculosis. The spleen and the liver were bound together with adhesions. The spleen was covered with spots about the size of a cent, which looked like cartilage. The spleen had a firm consistency and a reddish-brown appearance. The follicles were not prominent but the trabeculae were well developed. The liver was enlarged and had a firm consistency. The capsules of the kidneys were stripped with difficulty; chronic interstitial nephritis. Six small soft stones were found in the bladder.

*Microscopic Examination.* The bone-marrow of the sternum and the femur was the same. It contained increased connective tissue and was dominated by myelocytes and neutrophils. Many eosinophils. Rarely any basophils. There were a large number of polymorphonuclears and more than the normal amount of eosinophils. More lymphocytes were found in the sternum than in the femur and also an occasional giant cell.

The liver and pancreas showed myeloid rests.

Spleen: Sections all the same; not the usual picture. Had a great deal of myeloid tissue which consisted of myelocytes, polymorphonuclears, many eosinophils, and an occasional lymphocyte and red blood cell. No high degree of phagocytosis. Trabeculae more developed than normal.

Lymph glands: Myeloid rests.

Endocrine glands were negative.

This case was thought to be erythremia, but at necropsy it was a typical myelogenous leukemia. Hedinius believes that erythremia can become a leukemia or, it may be, a combination of the two diseases, and fall into a separate group between erythremia and leukemia. However, leukemia is not always combined with anemia but may be combined with a polycythemia.

This patient came in for her lung condition instead of the large spleen. During the last months the red blood cells increased to 11,540,000, but two months before death the patient had a pronounced anemia.

CASE OF ROSIN.<sup>77</sup> October 15, 1908. Woman, aged fifty-two years. For the past five years she has been troubled with congestion of the head, suffering from attacks of vertigo; face

flushed and burning of the eyes. She suffered of scintillating scotoma and severe attacks of headache of the opposite side; had five attacks of palpitation which lasted for hours, the last attack lasting for five hours. In recent years the patient has suffered three attacks of severe pain in the region of the left kidney, and during and after each attack the patient passed a quantity of gravel. Some of these attacks were only relieved after taking morphin. Up to this time the patient had been under the care of Freidrick Müller, who had made a diagnosis of polycythemia, the blood count being 10,000,000 red cells, and the patient had a large spleen. The patient had received hydrotherapeutic treatment for this condition, and during the renal attacks had gone to Carlsbad for treatment.

*Physical Examination.* Showed the patient to be in a state of poor nutrition. The skin and mucous membrane were normal and somewhat cyanosed. There was no edema or vascular changes; the conjunctivæ were slightly injected. The spleen was enlarged and extended downward to the umbilicus; the surface was smooth and the splenic incisure could be definitely felt a hand-breadth below the costal border. The spleen measured by palpation 27 x 16 cm. The liver was enlarged and extended below the costal border. The edge was rounded and tender to palpation. The kidneys were both palpable, the left in spite of the large spleen. They were both large, mobile and could be displaced. The heart was slightly enlarged; the pulse was 88 and soft. Lungs: The breath sounds were slightly accentuated over the right apex, probably within normal limits. Urine: Less than 1-10 per cent albumin.

*Blood Examination.* Red cells, 3,500,000 on two occasions, thus in no way increased. White cells: 48,000 to 52,000. Differential blood count showed 80 per cent polymorphonuclears; the remaining 20 per cent were made of 12 per cent eosinophils; 2 per cent lymphocytes; 6 per cent distributed among other cells, mast cells and mononuclears, which were granular.

One would make a diagnosis of leukemia if the previous history had been different. The differential count shows no myelocytes and does not resemble lymphatic or myelogenous leukemia. Rosin, however, thinks that the granular mononuclears might be looked upon as young myelocytes. With the previous history a number of complicating symptoms present themselves. Polycythemia had preceded the present picture several years. The patient now had a complete remission of the red cells, which are below normal, and a leukocytosis, which is not altogether a picture of leukemia, the blood showing no definite myelocytes.

CASE OF WINTER'S.<sup>102</sup> Man, aged forty-six years. Denies luetic infection. Had measles, otherwise previous medical history was negative. For the past six years the patient noticed redness

of the skin and at times cyanosis of the face and hands. He has also had attacks of weakness and vertigo. The splenic tumor was noticed at this time. The patient was advised to go to Carlsbad for treatment, which he did, and was temporarily improved. In September, 1904, the patient came under the care of Krause, of Jena, who on studying the blood diagnosed the case as chronic myelogenous leukemia, and gave him roentgen-ray treatment over the spleen and long bones. Blood picture, October, 1904: Hemoglobin 110 per cent. (Sahli); red blood cells, 4,800,000; leukocytes, 22,600; polymorphonuclears, 65 per cent; myelocytes, 30 per cent; a few small and large lymphocytes and an occasional eosinophil. No poikilocytosis. Five months after beginning of the roentgen-ray treatment, March, 1905, the following blood picture was found: Hemoglobin, 110 per cent (Sahli); red blood cells, 6,900,000; leukocytes, 9,800. The myelocytes had decreased from 30 to 8 per cent. The polymorphonuclears had increased to 90 per cent and the lymphocytes were 1 to 2 per cent. The splenic tumor at the beginning of the roentgen-ray treatment extended to the umbilicus and was quite hard. Under treatment it decreased in size considerably. In the succeeding years there was considerable improvement. In June, 1907, there were no particular symptoms. When the patient was weak he went to the country, where he rapidly recovered. At the end of June, 1907, Stern was consulted and he found the patient to be cyanosed; the peripheral arteries were sclerosed. The heart and lungs were negative. The spleen was enlarged to the umbilicus and to the midline. On palpation it was uneven and the incision was easily palpable. The liver was not enlarged. The nervous system was negative. There was no edema. The urine showed albumin, 0.5 per cent (Esbach). A few hyaline and granular rests. Blood pressure 123 mm. Hemoglobin (Riva Locci). Blood picture: Red blood cells, 8,292,000; white blood cells, 23,200; hemoglobin, 19.78 per cent (Fleisch-Miescher), 18.5 normal oxygen capacity. There were numerous normoblasts in November, 1907. The same condition as in June. No myelocytes found in a number of preparations. One megaloblast was found. Comments on the case by Winter: The polycythemia probably dates back six years, when Krause found the red cells about normal. Three months after the roentgen-ray treatment the red cells increased to 7,000,000 and the hemoglobin was 110 per cent. At the present time there is a more marked polycythemia. The splenic tumor is about the same size. In 1904 Krause found many myelocytes; since that time the myelocytes have considerably decreased and at times none were to be found. The lymphocytes were decreased. The polymorphonuclears and mononuclears were increased.

CASE OF NICOLA'S.<sup>56</sup> A. G. H., aged fifty one years, married, admitted April 27, 1908.

*Family History.* Father died of internal abscess at forty-five; mother died of inflammation of the bowels.

*Past-Medical History.* Negative. S. H. Does office-work.

*Social History.* Does office-work. Habits good.

*Personal Inspection* (three years). Developed periodic headaches about once a week. During the fall of 1907 these attacks became more severe, for which he was forced to take something to relieve them. During the attacks he suffered from vertigo and shooting pains. In December the attack lasted several days, with which he had a severe photophobia and there was also an extreme cyanosis of the face and neck. The headache and cyanosis never entirely disappeared after this attack, but the patient was able to be about, suffering, however, from exacerbations of his symptoms every few days. The patient had several of these major attacks. Denied any specific infection. The bowels were obstinately constipated.

*Physical Examination.* A well-developed male, 5 feet 9 inches tall, weighing 145 pounds net. Cyanosis of the face and neck; the mucous membrane of the mouth, eyes, injected. Hands blue. Spleen palpable, one inch below the costal border. The ophthalmoscope showed the veins of the fundus much dilated, blue and tortuous. Laboratory findings: total strength of the body, 3620 pounds as compared with 4385 pounds for the normal average man of the same height. Urine: usually normal. Feces negative. Blood examination: hemoglobin, 120 per cent; red cells, 8,000,000 white cells increased up to 250 per cent. Average blood-pressure, 137.5 systolic and 95.5 diastolic. Average pulse-rate, 78.8 The differential white blood counts showed a decrease in the small lymphocytes, 6.8 per cent. The polymorphonuclears and neutrophils were constantly increased, 84.5 per cent. The other normal elements were neither increased nor decreased. Of the pathologic elements myelocytes were uniformly present and constituted 1.6 per cent of the whole. The normoblasts were reported once in eight counts. Megaloblasts were reported three times and constituted 0.9 per cent.

During the patient's stay in the hospital the patient had recurring attacks of headaches, at which time he would become more cyanosed. On May 10, he had an attack of pain similar to angina pectoris, during which the cyanosis increased. On June 1 the patient developed pain in the calf of the leg resembling a severe sprain. The patient was also troubled with pruritus. Treatment was symptomatic: tonics, sprays, massage, mechanical vibrations, potassium iodide and later roentgen-ray radiation over the spleen. The patient improved under the treatment and went home feeling better. However, it was thought that it would be temporary and that his former symptoms would reappear.

CASES OF W. TÜRK, 1904.<sup>92,101</sup> CASE I. Woman, aged forty years. Headaches and pain in the first hypochondriac for one and one half years. Enlargement of the liver and spleen. Jaundice. Excess of urobilin and a little urobilin in the urine. Wasting. No cyanosis or special redness of the face. The red cells were about 8,000,000 and the white cells about 10,000. A few erythroblasts and a few myelocytes were present. Death with increase of jaundice and hemorrhage from the nose and alimentary canal. The red blood cells diminished in number to 5,160,000 before death. The necropsy showed cirrhosis of the liver with regenerative changes (multiple adenomata). The spleen was large, adherent to the liver and of firm consistency. The bone-marrow in the large bones was dark red in color and of a fairly firm consistency.

CASE II. Red cells, 9,965,000; white cells, 33,800; hemoglobin, 140 per cent. Polymorphonuclear neutrophils, 90 per cent; myelocytes, 0.1 per cent. The remaining cells were lymphocytes and occasional mast cells.

CASE III. Red cells, 9,670,000 to 8,430,000; white cells, 26,700 to 23,100. The differential count showed occasional myelocytes.

CASE IV. Red cells, 8,380,000; white cells, 16,500. Occasional myelocytes were found in the differential count.

CASE OF R. BLUMENTHAL<sup>4</sup> (1907). Woman, aged thirty-one years. From two years of age she was subject to attacks of paroxysmal dyspnea accompanied by severe headache and followed by copious expectoration. From the age of twenty-one years the patient had cyanosis, debility and occasional hemorrhages. Red blood cells, 11,450,000; white blood cells, 16,300, of which 36 per cent were myelocytes. There were no nucleated red cells. Hemoglobin, 110 per cent. The appearance of the patient's face somewhat resembled that of patients with Graves's disease, but in addition it was extremely congested. By ophthalmic examination the retinal veins were seen to be tortuous and engorged with blood. The necropsy showed fibrous adhesions of the right pleura and bronchopneumonia of the lower lobe of the left lung. The bronchial lymphatic glands were very large and of a reddish-brown color. There was a remarkable varicose condition of the veins of the dura mater and a small hemorrhage was found in the hypophysis cerebri. The heart was somewhat hypertrophied. The capsule of the liver was thickened in places. There was no disease of the kidneys. The bone-marrow from the shaft of the humerus was red and succulent like fetal marrow; on microscopic examination the leukoblastic tissue was found to be markedly in excess

of the erythroblastic tissues. Microscopic examination of the enlarged lymphatic glands showed great richness in the blood-vessels and congestion and fibrosis. Microscopic examination of the liver showed passive congestion and some increase in the interacinous connective tissue. Microscopic examination of the spleen gave no evidence of erythroblastic or myeloid transformation. Blumenthal regards the case as probably of congenital origin. The case is remarkable for the excessive leukoblastic activity, evidenced by the large number of myelocytes in the circulating blood and the results of the microscopic examination of the bone-marrow after death. It should be remembered that though the leukoblastic was decidedly in excess of the erythroblastic tissue, yet owing to the fetal condition of the bone-marrow in the shafts of the long bones (normally occupied by fatty marrow) the amount of erythroblastic tissue in the body must have been greatly in excess of normal.

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## PACHYMEINGITIS HEMORRHAGICA INTERNA: A STUDY OF FIVE CASES OF NON-TRAUMATIC HEMORRHAGIC SPINAL FLUID.

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My justification for the presentation of the following case summaries with comment lies in the conviction that the condition of pachymeningitis hemorrhagica interna is rarely diagnosed and that thus an occasional opportunity for the physician to be of real therapeutic use is missed. Pachymeningitis hemorrhagica interna, or *hematoma of the dura mater*, is a common finding in the postmortem material from institutions devoted to the care of chronic nervous and mental disorders and of the aged. At the Pathological Institute in Vienna we were frequently shown hematomata of the dura mater, but they were considered to be of pathological rather than of clinical interest. The finding is stated to be common in general paralysis, alcoholism, senile dementia, arteriosclerosis, hemorrhagic diathesis, etc., and "is for the most part an accidental affection."<sup>1</sup> The diagnosis is rarely made.<sup>2</sup>

Dieulafoy<sup>3</sup> describes its symptoms, says little about diagnosis, but hints at the value of lumbar puncture by saying that it is an interesting question.

Jelliffe and White<sup>4</sup> describe the disease, give nothing tangible in the way of diagnosis, and do not even mention lumbar puncture as a diagnostic or therapeutic procedure.

Edwin Bramwell<sup>5</sup> says: "A clinical diagnosis is rarely made, and even when recognized during life it is doubtful whether therapeutic measures have any distinct influence in arresting its progress. Indeed, during the past thirty years little of material importance has been added to our knowledge of the disease."

The pediatricians<sup>6</sup> have noted the disease frequently and have formulated a diagnosis based on (1) a bloody spinal fluid, (2) rapidly developing hydrocephalus, and (3) hemorrhages into the fundi. Puncture of the fontanelle, which commonly bulges, has lead to a diagnosis in the presence of a clear spinal fluid. Grüneberg<sup>7</sup> reported a case substantiated by autopsy in a one and one-

<sup>1</sup> Oppenheim: Text-book of Nervous Diseases, English translation, Edinburgh, 1911, p. 744.

<sup>2</sup> Edwards, Arthur L.: Principles and Practice of Medicine, Philadelphia and New York, 1916.

<sup>3</sup> Pathologie Interne, Paris, 1911, I and III, 759.

<sup>4</sup> Diseases of the Nervous System, Philadelphia, 1917.

<sup>5</sup> Osler's Modern Medicine, Philadelphia, 1910, 7, 166.

<sup>6</sup> Rietschel: München. med. Wehnschr., April, 1912.

<sup>7</sup> München. med. Wehnschr., May 21, 1918.

half-year-old child. Bulging of the fontanelle is considered one of the most significant symptoms by Hahn.<sup>8</sup>

**The Pathology and Pathogenesis.** The controversy as to whether the inflammatory membrane is primary and the hemorrhages secondary, or whether the hemorrhages are primary, has been waged periodically for half a century, and as far as can be judged from the literature has not yet been decided to the satisfaction of all. Grossly, we find on the inner surface of the dura, especially on the convexities, deposits of more or less transparent detachable membranes stained red, brown or reddish-brown by blood pigment. These membranes often lead to tremendous thickening of the dura. Hemorrhagic stratification is commonly seen, the color and consistency of the various strata indicating their respective ages. With time more or less complete organization of the lamellæ takes place. George B. Hassin<sup>9</sup> reports 2 cases of hypertrophic pachymeningitis, 1 with hemorrhage, which from a histological standpoint were syphilitic. Based on the study of these 2 cases Hassin concludes "that the sole cause of the lesion is syphilis, and that there is a simultaneous involvement of all the three membranes, including the brain tissue proper."

**CASE I.**—A paretic was seen in 1908, with Dr. Paul Ellis, for a coma preceded by convulsions. The significant findings were moderate rigidity of the neck, Kernig's sign and muscle hyperesthesia, which was most marked along the spine. To our surprise a lumbar puncture revealed a uniformly bloody fluid which came under high pressure. There was no history of trauma and no paralyses could be made out. On the basis of the bloody spinal fluid a diagnosis of pachymeningitis hemorrhagica interna was suggested because a hemorrhagic spinal fluid had been found in a paretic. The autopsy showed fresh subdural hemorrhages covering most of the right occipital region, with several fresh punctate hemorrhages scattered over the cortex. The falling together of paresis, bloody spinal fluid and symptoms of meningeal irritation had led to a correct presumptive diagnosis.

**CASE II.**—M. K. (June, 1915), aged eighteen years, suddenly went blind on the street and was at the same time seized with a "terrific" headache. There was no history of trauma. She was able to walk two blocks to the office where she worked. On arrival there "her head went back", and she vomited and lapsed into a variable state of stupor which persisted throughout the afternoon. Six hours after the onset the patient was seen in a deep coma, from

<sup>8</sup> Klinischer Beitrag zur Lehre von der Pachymeningitis hemorrhagica interna in frühen Kindesalter, München. med. Wehnschr., August 17, 1911.

<sup>9</sup> Histogenesis of Cerebral Hypertrophic Pachymeningitis and its Relation to Syphilis, Am. Jour. Syph., September, 1918, 2, 715.

which she could not be aroused; her neck was rigid; the tendon and superficial reflexes were gone; Kernig's sign was present; there was conjugate deviation to the left. Lumbar puncture brought a uniformly bloody fluid under extreme pressure. About 70 cc were removed. A few moments after the puncture the patient could be aroused sufficiently to answer simple questions. The spinal fluid and blood Wassermann tests were negative. Cultures were not made, but smears stained for bacteria were negative. The leukocyte count was 13,000. The urine examination was negative. Lumbar puncture during the following days showed a rapid transition from a reddish to a brownish and finally to a yellowish fluid. Chemical tests for hematin were positive in these fluids. The pressure of the spinal fluid rapidly returned to normal. The fundi examined several days after the onset were normal.

Severe headache, mental wanderings, muscle cramps, muscle pain, hyperesthesia, hyperacusis and slight febrile manifestations, without definite cerebral localization phenomena, prevailed in the early days of the convalescence, which was complete at the end of four months. The patient has had no recurrence of the trouble and is well six years after the attack.

Lumbar puncture in this case may almost be said to have been life-saving. Each reduction of intraspinal pressure brought definite alleviation of the headache, the stupor, muscular pains, cramps and stiffness.

The only antecedent etiological factor was a chronic maxillary sinus disease due to dento-alveolar infection. An acute suppurative maxillary sinusitis which required drainage through the mouth and subsequent curettement of polypi had followed the removal of a tooth about one year before the cerebral insult. The sinusitis had been considered cured for eight months prior to the cerebral affair, and has since remained so.

CASE III.—A. P., widow, aged forty-eight years, had enjoyed excellent health up to the current illness. There was no history of trauma. She was taken ill suddenly with an intense pain in the back of the head and neck, which was quickly followed by general convulsions. She was unconscious for several hours. When seen, twelve hours after the insult, the patient lay on her back with her head drawn slightly backward. She was conscious. The important physical findings were rigidity of the neck, extreme muscle hyperesthesia, the patient crying out when moved, a well-marked Kernig's sign, slight right facial weakness, protrusion of the tongue slightly to the right, absent abdominal reflexes, exaggerated knee-jerks and ankle-jerks, with a suggestion of Babinski's and Oppenheim's signs on the left side. The fundi were normal. The pulse was 84; the systolic blood pressure was 190. The urine examination was negative. The leukocyte count was 12,000. Lumbar puncture

brought a uniformly bright, bloody fluid under increased pressure. The Wassermann tests of both spinal fluid and blood were negative. Protein and colloidal-gold tests were unsatisfactory on account of the admixture of blood. The number of white cells seemed proportional to the amount of blood. Cultures and smears of the spinal fluid stained for bacteria were negative. The spinal fluid four days later was brownish in color but still under increased pressure. During a period of three weeks there were four apoplectic insults with convulsions and coma followed by marked exacerbation of the headache. Fresh blood was always found a few hours later in the spinal fluid. Febrile manifestations, delirium, hallucinations, stupor, headache, hyperacusis, hyperesthesia, restlessness, irritability, insomnia, emaciation and extreme asthenia were prominent features in a severe illness which required ten weeks of hospitalization. Convalescence was slow and the patient did not regain her normal state for eight months.

The noteworthy features in this case were the registration of fresh cerebral hemorrhages in the spinal fluid after each cerebral insult, the improvement in the well-being of the patient following lumbar puncture, and the rapid hemolysis of the red corpuscles in a spinal fluid, which changed rapidly (a matter of two or three days) from a red to a brown and then to a bright yellow. There were no apparent etiological factors unless one could impugn an extensive buccal infection, which was removed during the convalescence, and an essential hypertension. The patient was not an alcoholic, not a paretic, not a dement, nor a senile. She suffered from no chronic disease, except an essential hypertension, the systolic blood-pressure varying from 150 to 200. There has been no recurrence of the trouble during four years. She is reported to still have hypertension, with systolic blood-pressure 235, diastolic 160, and suffers occasionally from headache. Otherwise her health is stated to be excellent.

CASE IV.—H. D., male, aged fifty-four years, was seized suddenly while going to bed with a terrible pain in the back of the neck and head. There was no history of trauma. There were no convulsions. The illness was attributed to a wild duck dinner eaten a few hours prior, which was vomited. Physical examination twelve hours later showed rigidity of the neck, paravertebral deep hyperesthesia and exaggerated ankle- and knee-jerks. Babinski's and Oppenheim's signs and ankle-clonus were present on the left side. The tongue was protruded slightly to the left and there was a slight left-sided facial paralysis. Kernig's sign was absent. The fundi were normal. The pulse was 60; the temperature was 100°; the leukocyte count was 8800; the blood-pressure was systolic 150, diastolic 80; the urine examination was negative. The spinal fluid came under greatly increased pressure; it was uniformly bright red. The

white cells were no more numerous than they should be with the amount of blood. Cultures and smears stained for bacteria were negative. The blood and spinal fluid Wassermann tests were negative.

The relief of the headache following lumbar puncture was notable. Later punctures showed the brownish fluid fading to yellow seen in all of the cases. There was a second insult which was corroborated by a fresh hemorrhage in the spinal fluid. Convalescence was slow and the patient did not regain his usual health for one year, but is in normal health three and one-half years following the attack. The only tangible etiological factor was a mild diabetes mellitus which the patient had controlled by diet for two years. Ten years prior to the above-mentioned trouble the patient had suffered a diffuse peritonitis with an abscess in the left lumbar gutter, probably from a diverticulitis of the sigmoid. There was no appreciable degree of arteriosclerosis.

CASE V.—C. B., farmer, single, aged forty-four years, came to St. Joseph's Hospital, Omaha, Neb., in February of 1918, complaining of pain in the back, neck and legs, and stiffness of the back and neck with headache. The onset had been gradual without apoplectic insult. There was no history of trauma. Examination showed a well-developed muscular man without materially disturbed sensorium or psyche. There was marked rigidity of the neck, muscle hyperesthesia and spasticity and Kernig's sign. The tendon reflexes were exaggerated. Babinski's sign was present on both sides. There were no definitive localization phenomena. The fundi were normal. The pulse was 56. The systolic blood-pressure was 150 and the diastolic 90. The temperature was 100° F. The leukocyte count was 16,000 with 80 per cent polymorphonuclears. The urine examination was negative. Lumbar puncture brought a uniformly bright, bloody fluid with increased pressure which on subsequent punctures showed the typical brownish-fading-to-yellowish discolorations. The Wassermann tests of blood and spinal fluid were negative. Cultures and smears of the spinal fluid stained for bacteria were negative. The lumbar punctures seemed to have a decidedly beneficial effect on the symptoms. Convalescence was complete in seven weeks. The patient is in perfect health three years after the onset.

No noteworthy illnesses preceded the trouble. The patient, however, had been in a hospital one year prior for what he stated was a heart and kidney affection, during which time his tonsils had been removed. There was no evidence of cardiovascular trouble.

The symptomatology of the above cases shows a striking uniformity. *Headache* was always present at the beginning. Its onset was sudden and it was described as terrific or terrible; it was located



mostly in the occipital and basal regions, and in the neck. Relief from lumbar puncture was immediate. The contemporaneous recurrence of severe headache and fresh blood in the spinal fluid was noteworthy. Headache was often carried well along into convalescence. These later headaches were not severe but were complained of as a dull, sore feeling. They were aggravated by moving the head and by fatigue. *Rigidity of the neck* was a constant symptom, and with its associated manifestations of *spinal nerve-root irritation* such as hyperesthesia, especially deep muscle tenderness, muscular rigidity, Kernig's sign, deep paravertebral tenderness, etc., constituted the *second member* of a diagnostic triad. In two of our cases the deep hyperesthesia was so intense that the patient could not be moved without crying out. Muscle cramps were common and often very severe. Muscle stiffness and soreness persisted long into the convalescence and was usually the last symptom to disappear. Relearning to walk was made more difficult by the muscle stiffness. *Lumbar puncture*, the *third member of the triad*, furnished the most important diagnostic sign, a bloody spinal fluid, with characteristic changes from day to day from a bright red, bloody fluid containing well-formed red blood corpuscles to a brown and finally a pale yellow fluid without corpuscles or shadows. It is to be noted that in our cases every fresh insult or exacerbation of symptoms was followed by the appearance of fresh blood in the spinal fluid. Why lumbar puncture has not attained the pre-eminence which it deserves in the diagnosis and treatment of this disease is somewhat strange. Oppenheim<sup>10</sup> says: "In doubtful cases lumbar puncture may enable one to decide." This author considers the results indecisive and places more reliability on skull puncture. Dreyfus<sup>11</sup> strongly recommends spinal puncture both as a diagnostic and therapeutic aid.

The importance of a uniformly bloody fluid as a diagnostic sign may be best appreciated by a consideration of the common causes of bloody spinal fluid. In hemorrhage from needle trauma, samples taken at intervals during the puncture are not uniformly bloody, and the first sample always carries the largest quantity of blood. Furthermore, the blood from puncture trauma coagulates in the bottom of the tube.<sup>12</sup> After we have excluded puncture hemorrhage we have to consider hemorrhages from (1) intracerebral lesions; (2) trauma; (3) diseases of the meningeal vessels, such as arteriosclerosis and aneurysm; and (4) pachymeningitis hemorrhagica interna. In order for the blood to appear in the spinal fluid from an intracranial lesion it must spill either into the ventricles or into the subarachnoid space, from which the cells rapidly diffuse throughout

<sup>10</sup> Loc. cit., p. 747.

<sup>11</sup> Pachymeningitis cerebrale hemorrhagica, München. med. Wchnschr., November 13, 1914.

<sup>12</sup> Oppenheim, Dreyfus, Loc. cit.

the water bath enveloping the cerebral axis. Blood from a cerebral hemorrhage or hemorrhage into a tumor would reach the spinal fluid only insofar as it penetrates the subarachnoid space or the ventricles. Hemorrhages into the internal capsule sufficiently severe to satisfy either of the above conditions are usually rapidly fatal. Furthermore, the resultant paralyses are usually very definite if the patient survives the original insult. The previous clinical course should establish the diagnosis in cases of hemorrhage from a glioma. Hemorrhage from trauma can be excluded by the history and the physical and roentgen-ray examinations. Hemorrhages from small aneurysms and following arterial changes in the meningeal arteries would seem impossible to differentiate from pachymeningitis hemorrhagica interna, for clinically they equal the same thing. Protein and colloidal-gold tests have proved of no value in our cases on account of the admixture of blood serum. White cell counts are obviously of little value in the presence of considerable quantities of blood. *It is to be noted that in only 1 of 5 cases was there any evidence of syphilis as an etiological or symptomatic factor.*

**Secondary Symptoms and Findings.** Symptoms of irritation or destruction of the upper motor or sensory neurons such as paralyses, pareses, convulsions, Jacksonian epilepsy, exaggerated tendon reflexes, disturbed superficial reflexes (positive Babinski, Oppenheim, absent abdominal reflexes, etc.), disturbed psyche and sensorium, etc., are merely phenomena which mirror the localization and severity of the process. The absence of residual paralyses is noteworthy. Choked disk and retinal hemorrhages are frequently noted in the literature. They were absent in our cases, which was probably due to the fact that all of our cases save one were punctured within twelve hours of the onset, and that subsequently the intracranial pressure was not allowed to increase much beyond the normal insofar as it could be reduced by repeated lumbar punctures. A moderate polymorphonuclear leukocytosis was commonly present. This might be assumed to speak for the infectious nature of the disease did not such a leukocytosis occasionally occur in intracranial hemorrhages of different origin. The persistence of muscle cramps and stiffness, fatigability, instability, restlessness and insomnia late into convalescence in our cases is noteworthy.

**Conclusions.** Headache, sudden in onset, with signs of meningeal and spinal-root irritation when associated with a uniformly bright, bloody spinal fluid, is suggestive of pachymeningitis hemorrhagica interna.

In this disease repeated lumbar puncture has proved a measure of therapeutic value.

**DIAPHRAGM IRREGULARITIES (PRELIMINARY CONTRIBUTION).**

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DURING the course of the examination of registrants prior to entrance into military service at Camp Lewis, considerable numbers with lung abnormalities, including what was considered obsolete or healed tuberculosis, were accepted for military service by the Tuberculosis Board.

Careful records, including physical examination and roentgen-ray findings, were made of more than 40,000 out of the 174,212 soldiers examined by the board on entrance into service, during service and prior to separation from service. These records included all cases in which tuberculosis was suspected either from the general condition of the registrant, his past or present history or from the results of the physical or roentgenological examination.

In order to check up our judgment in accepting registrants with lung abnormalities for service, especially those who had what we thought was healed tuberculosis of no military importance, we decided, among other methods of control, to examine every soldier who had been in the base hospital on account of measles, whooping-cough, influenza, pneumonia, bronchopneumonia and other acute respiratory infections. These men were examined at once after discharge from the base hospital, again at the end of a month, and we endeavored to make a third examination approximately two months later. Of course, not all soldiers were available for the three examinations. However, we followed 3754 cases of the above character who had been in the base hospital during their stay at Camp Lewis, and later during demobilization we were in a position to compare their examination on entrance into service and examination made after discharge to duty from the base hospital, with the physical examination made prior to separation from service. In addition to the above we were able to compare the entrance and demobilization examinations of an additional 6064 cases, who had not been in the base hospital but who presented lung abnormalities on entrance into military service. These examinations revealed diaphragm irregularities under the fluoroscope and on the plate in 4 per cent of all cases studied.

Heretofore irregularities of the diaphragm having a tented appearance have been thought to be due to pleuro-diaphragmatic adhesions. However, in checking up examinations made at various times on the same cases some observations were made which were inconsistent with the assumption that tenting of the diaphragm necessarily meant pleuro-diaphragmatic adhesions.

The following case is a typical example of observations which prompted this clinical study:

J. H. B., aged twenty-two years, private in the infantry, was examined June 28, 1918, upon his arrival at Camp Lewis for military service. The fluoroscopic examination showed the diaphragm regularly curved, phrenico-costal angles clear, good excursion and no delay. On November 26, 1918, he received his first examination after discharge from the base hospital, where he had been confined two months on account of an influenza-bronchopneumonia of the lower lobe of the right lung. The fluoroscopic examination at this time showed "delayed diaphragm excursion on the right side with tenting of the middle third at the termination of the hili-diaphragm superficies. This was attributed to pleuro-diaphragmatic adhesions, the result of his previous bronchopneumonia. He was examined again after one month, showing practically the same findings. The third examination was made three months later, and while the report stated there was some exaggeration of the hilus and hilidiaphragm superficies, no remark was made regarding tenting of the diaphragm.

As similar findings had been noted in other cases, it appeared that either the fluoroscopist was overlooking abnormalities or failing to dictate them to the stenographer who took the dictation in the dark room or the stenographer was careless in taking or transcribing his notes. Therefore to determine, if possible, where the fault lay the case referred to (J. H. B.) and some other cases wherein errors were thought to have occurred were called up for examination, as a result of which the correctness of the findings of the last previous fluoroscopic examination was confirmed. In the case of J. H. B. no tenting of the diaphragm was found upon reëxamination. Case records were gone over and other cases of the same character were studied anew, and it was found that many individuals presenting tenting of the diaphragm on one examination showed no tenting at subsequent examinations made after an interval of several months.

Accordingly the inference that pleuro-diaphragmatic adhesions were responsible for all these irregularities of the diaphragm characterized by tenting was no longer consistent, because in many cases the irregularity disappeared, which would not have been the case were pleuro-diaphragmatic adhesions the cause.

After some study the following theory suggested itself as a logical explanation for the occurrence of the type of diaphragm irregularity appearing as a tenting at the termination of the hili-diaphragm superficies which we had seen disappear during the course of our fluoroscopic examinations covering a period of several months.

The lower bronchial branches may be likened to rubber tubes stretching and contracting as the lung expands and contracts in response to a downward pull and rise of the diaphragm (Fig. 1). During the course of acute and chronic respiratory infections, wherein infiltrative and proliferative changes occur in the bronchi and peribronchial tissues, the normal elasticity of the bronchi is diminished. If these changes are slight and do not extend to the superficies the downward pull of the diaphragm may be only delayed or retarded (possible explanation of Williams's sign), or if the process has extended to the finer bronchi and is of a diffuse nature the diaphragm frequently assumes a wavelike irregularity. However, in cases in which the bronchial and peribronchial changes are more extensive and involve the respiratory bronchioles situated

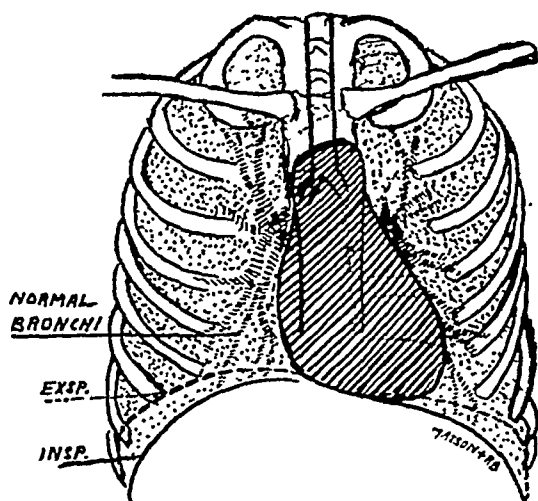


FIG. 1.—Normal diaphragm excursion. Bronchi stretching and contracting, permitting bases of the lung to follow the diaphragm upward and downward.

close to the basal pleura the downward pull of the diaphragm meets with response on the part of the lung base everywhere except over the area served by the branches involved, frequently the termination of one of the lower lobe bronchial branches. Over this area the diaphragm fails to pull the lung downward, or at least not to the extent it does elsewhere. Accordingly that area of the lung base to which the bronchus leads is more or less fixed by the rigid bronchus, which acts as a buried suture extending from the hilus to the basal pleura. The negative intrathoracic pressure holds the diaphragm firmly to the lung. Consequently, during inspiration traction of the bronchus resisting diaphragmatic pull produces a dimple on the surface of the base of the lung. The diaphragm, being unable to pull the lung down at this point or separate from it, must necessarily mold itself to the irregular

contour of the base of the lung and is therefore sucked into the dimple, thus presenting a tenting which we will designate pseudo-adhesion.

The idea that the intrathoracic negative pressure is sufficient to suck the diaphragm into a lung dimple is supported by Sahli's explanation of Litten's phenomenon, which according to Sahli is due to suction exerted upon the intercostal spaces as the diaphragm begins to peel off the thoracic wall in its descent. The fact that the soft parts of the thoracic wall are sucked in during inspiration by the "peeling off" of the diaphragm, which tends to create a vacuum, leads us to believe that the intrathoracic negative pressure is sufficient to hold the diaphragm firmly to the lung and conform it to the contour of the surface of the lung base with

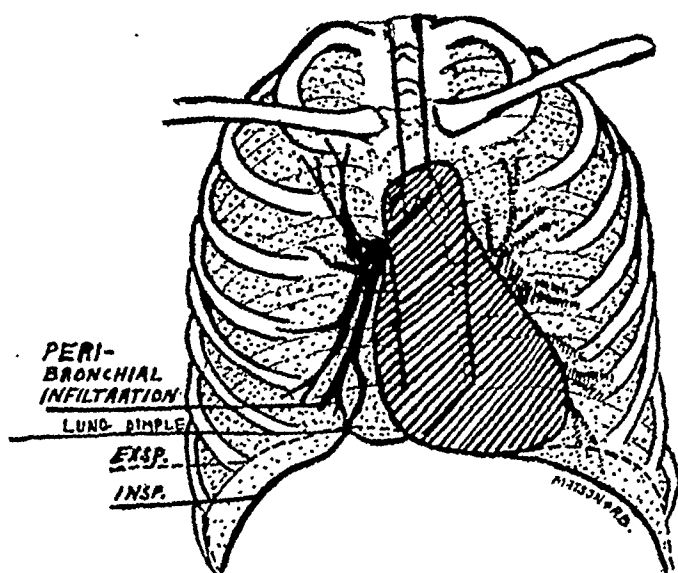


FIG. 2.—Mechanism of diaphragm irregularity due to negative force holding the diaphragm in a lung dimple.

which it comes in contact (Fig. 2). These irregularities due to pseudo-adhesions appear to be more marked in the asthenic types in which the diaphragm has undergone atrophy and suffered loss of tonus as has the other musculature.

Anatomical support for the theory above advanced was found in the following case coming to autopsy at General Hospital 21, Denver, Colorado, during my service there.

H. J. N., aged twenty-nine years, private in the infantry, had pneumonia in November, 1917 (side not stated), and made an apparent full recovery. He again entered a hospital with "pneumonia" June 4, 1918, and was continuously hospitalized thereafter, being transferred to General Hospital 21, April 21, 1919,

with a diagnosis of chronic active fibrocaseous tuberculosis of the upper lobe of the left lung.

For the purpose of this paper it will be sufficient to quote only the roentgen-ray findings referring to the diaphragm in this case. The roentgenological examination of May 1, 1919, states:

"The diaphragm on the left side presents marked tenting in the midclavicular line due to pleuro-diaphragmatic adhesions" (Fig. 3). Subsequent examinations made on September 20 and December 20, 1919, showed no change in the diaphragm irregularity. Exitus took place February 2, 1920.

The only part of the autopsy report which concerns the subject under consideration is the pathological findings of the left lung and the diaphragm:



FIG. 3

"Autopsy revealed the left lung adherent at the apex to the dome of the thorax and to the pericardium above. The base of the lung was smooth and glistening and no adhesions to the diaphragm were present. The cut section of the lung showed several cavities in the upper lobe with disseminated tubercles in the lower lobe. The lower lobe bronchial mucosa was studded with tubercles to within one-half inch of the pleura. The lower lobe bronchi showed marked connective-tissue proliferation with peribronchial infiltration extending to the diaphragm."

Diaphragm irregularities due to pseudo-pleuro-diaphragmatic adhesions appear in general, from the limited material studied, to be the sharply defined, angulated tentings occurring at the termination of the ramifications of the lower lobe bronchi, the tenting frequently being an apparent continuation of the bronchus. On the other hand those irregularities which are diffuse, not so clear

cut, nor so angulated and not so closely related to the bronchial ramifications and not following the anatomical course of the bronchi appear to be due to pleuro-diaphragmatic adhesions.

The case outlined above is the only one having an irregularity thought to be due to pseudo-adhesions which we have had an opportunity to study at autopsy. However, the utilization of artificial pneumothorax for differential diagnostic purposes has furnished information of a nature confirming the theory advanced. During the past six months we have been able to study 8 patients presenting diaphragm irregularities having the characteristics we have associated with pseudo-adhesions. The procedure carried out was the introduction of sterile air into the pleural cavity to release the suction or at least to reduce the intrathoracic negative pressure. All cases were fluoroscoped and stereoscopi-



FIG. 4.

cally plated beforehand, at once after and every few days for two weeks or more. In some cases the air was introduced while the patient was studied under the fluoroscope.

Of the 8 cases studied we believe 6 are pseudo-adhesion cases. The following case is typical of the 6:

L. B., aged seventeen years, was first seen February 12, 1918. Her chief complaint was cough and expectoration dating from an attack of whooping-cough followed by pneumonia four years previous. She had never complained of pleurisy. The physical examination was negative. The roentgen-ray plate (Fig. 4) showed slight exaggeration of the hilus shadows with increased density of the lower lobe bronchi, more marked on the left side. There was a tenting of the diaphragm at the termination of the hili-diaphragm superficies on both sides. The patient was seen



again August 16, 1920. The physical examination was negative. The roentgen-ray examination revealed no changes from the examination two and one-half years previous. According to my

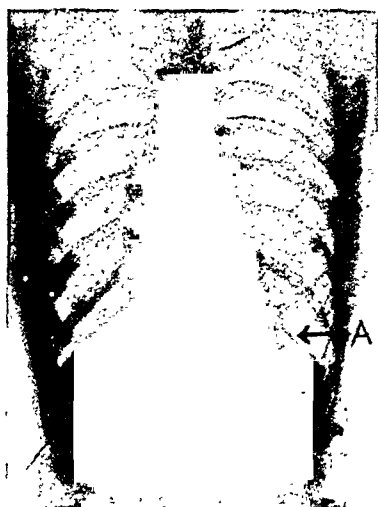


FIG. 5

new conception regarding diaphragm irregularities this case had an irregularity presenting characteristics of the psuedo-adhesion type. For differential diagnostic purposes the introduction of a



FIG. 6

small quantity of air into the left pleural cavity was decided upon. Accordingly a pneumothorax needle was introduced and the manometer recorded a negative pressure  $1\frac{1}{2}$  to  $3\frac{1}{2}$ . Sterile air was

introduced without pain under fluoroscopic observation. As the air flowed in the irregularity of the diaphragm gradually disappeared, being entirely absent after 250 cc of air had been introduced, at which time the intrathoracic pressure measured  $1\frac{1}{2}$  to  $2\frac{1}{2}$ . The plate made immediately afterward revealed a regularly curved diaphragm and the tenting had completely disappeared



FIG. 7.—Before expansion.

(Fig. 5), yet the quantity of air was so small that it was only apparent at the dome of the thorax; nevertheless it was sufficient to release the suction between the diaphragm and the lung. Fluoroscopic examinations were made at intervals of every three days. As the air absorbed the tenting reappeared, being marked at seven days, and at the end of ten days the tenting was apparently no different than previous to the air introduction (Fig. 6).

This, of course, does not prove that the tenting seen on the screen and plate of this and other cases was not due to adhesions, as light adhesions could easily separate without pain or without increasing the irregularity. But it is improbable that they would separate after so small a quantity of air and before other non-adherent air-containing parts of the lung had shown some sign

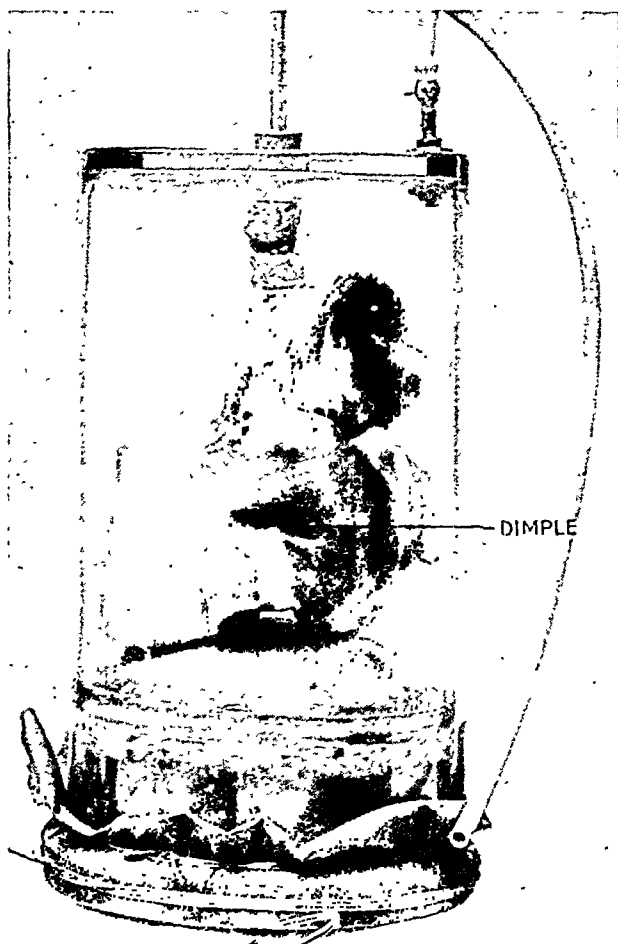


FIG. 8.—After expansion. Front view of large dimple.

of collapse. Furthermore, it is not likely they would reorganize so firmly after separation in a matter of a week as in the above case and produce a tenting of identically the same character and extent as the original one. Moreover, an irregularity due to pseudo-adhesions would be expected to reappear at the same site after restoration of the previous intrathoracic negative pressure. This occurred, as a matter of fact, in every case of pseudo-adhe-

sions. It is therefore not thought that pleuro-diaphragmatic adhesions were present in the above case, but that the negative intrathoracic pressure sucking the diaphragm to the irregular basal surface of the lung was responsible for the irregularity seen.

The principles concerned in the production of the lung dimple upon which diaphragm irregularities of the pseudo-adhesion type



FIG. 9.—Side view of large dimple.

depend were tested out experimentally, as shown in Figs. 7, 8, 9, 10, 11.

A bell jar was fitted with an inlet and an outlet at the top. In the inlet there was a rubber stopper through which passed a glass tube from which a pair of sheep's lungs was suspended by slipping the trachea over the glass tube and holding it securely in position

by ligation. There was a stop-cock in the outlet through which the air in the bell jar could be exhausted by suction.

The base of the jar had two diaphragms, one of thin rubber three inches from the base held in position by means of a wooden hoop and sealed air-tight. The second diaphragm, also air-tight, was at the base and was made of heavy rubber, in the center of



FIG. 10.—Before expansion.

which was a lug by means of which traction could be made downward, thus pulling the upper diaphragm down by suction (Fig. 7).

For the purpose of rendering a bronchus rigid a fine steel wire with a barb at the end was passed through the inlet down through the trachea into one of the finer bronchi and fixed by imbedding the barb in the wall of the bronchus.

As the air in the bell jar was exhausted, air from the outside

passed through the inlet into the lungs, which expanded regularly; the barbed wire, not being fixed above, permitted the bronchus to stretch as usual, the wire being pulled downward as the lung expanded. After the lungs partially expanded the barbed wire was fixed at the inlet and the lungs fully expanded by further suction. Added expansion took place everywhere except over

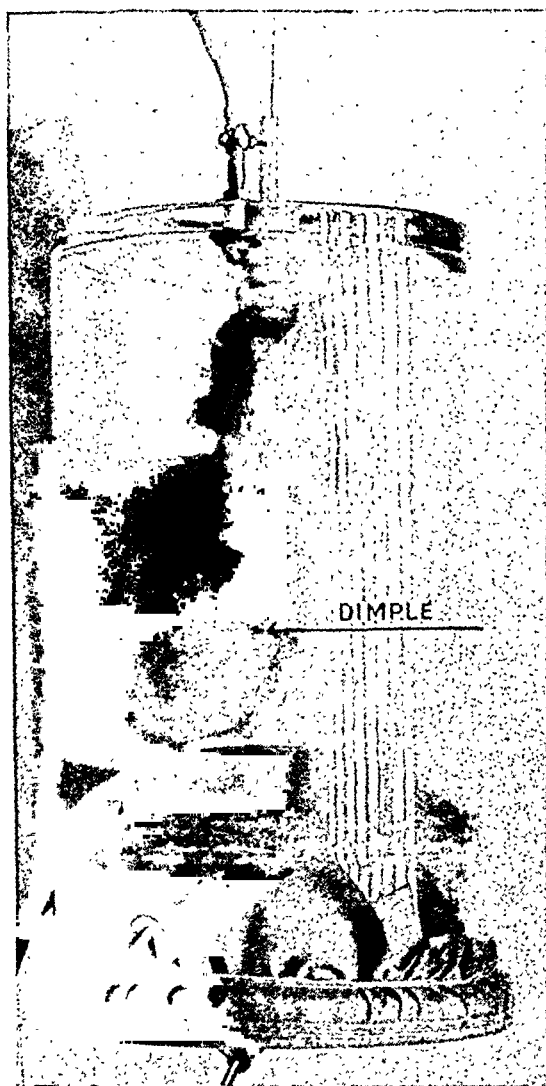


FIG. 11.—After expansion. Small dimple.

the site of the bronchus fixed by means of the barbed wire (Fig. 8 front view, Fig. 9 side view of dimple). This dimpling was increased and diminished by manipulation of the diaphragm stimulating inspiration and expiration.

It was proved that the size of the dimple depended upon whether the barb was imbedded remotely from the finest ramifications, thus fixing a large area of lung surface, served by that portion

of the bronchus which came off distal to the barb and producing a large dimple (as Figs. 8 and 9), or if the barb was imbedded in a terminal bronchus the dimple was correspondingly smaller (Fig. 10 before expansion, Fig. 11 after expansion).

It is appreciated that these experiments do not reproduce conditions thought to be responsible for dimpling of the lung. Nevertheless, they furnish material support for the theory advanced.

It was hoped by means of the upper thin diaphragm to reproduce the tenting of the diaphragm. However, the distribution of the bronchi and the character of the basal surface of the sheep's lungs did not permit producing a dimple at a point where it was possible for the rubber to fit itself into the dimple.

Further experiments are in progress and will be reported later.

**Conclusions.**—1. The assumption that tenting of the diaphragm always diagnosticates pleuro-diaphragmatic adhesions is unjustifiable.

2. Tentings of the diaphragm, frequently seen on plate and screen at the termination of the hili-diaphragm superficies with characteristics, which are associated with pseudo-adhesions, are purely physical phenomena brought about by two factors: (a) During inspiration the diminished elasticity or rigidity of the lower bronchial branches prevents descent of that area of the lung base in immediate relationship to the bronchus involved; thus a dimple effect is produced on the surface of the base of the lung. (b) The diaphragm being molded to the base of the lung by a negative intrathoracic pressure is held by suction in the dimple above referred to, producing a tented appearance (pseudo-adhesion).

3. Diaphragm irregularities of the pseudo-adhesion type are commonly found during the course of acute and chronic respiratory infections. In acute respiratory infections with peribronchial infiltration involving the lower bronchial branches the irregularity disappears with *restitutio ad integrum*. In chronic respiratory infections with consequent connective tissue, proliferative changes in the lower bronchial ramifications, the irregularity appears to be permanent in nature.

4. It is reasonable to suppose that should infiltrative or proliferative changes incident to infection not halt at a point in the bronchial tree proximal to its termination, but, instead, proceed to the pleura, then the diaphragm would become adherent and the pseudoadhesion would be converted into a true adhesion.

It is hoped that this contribution will excite interest and further study of the subject.

## ANEURYSM OF THE LEFT VENTRICLE.

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New York City.)

ANEURYSM of the left ventricle is a rare condition. In 1757 Galeati<sup>1</sup> and John Hunter<sup>2</sup> each reported a case in which the apex of the left ventricle was involved. In 1785 Walter described an aneurysm almost as large as the heart itself.<sup>3</sup> Thurnam, in 1838, collected a series of 66 cases, 27 of which were at the apex and 39 elsewhere over the left ventricle.<sup>4</sup> Legg, in 1883, collected 88 additional cases, of which 57 were at the apex.<sup>5</sup> Twenty years later Hall collected 112 cases, of which 92 involved the left ventricle. Most of these aneurysms were localized at or near the apex of the heart.<sup>6</sup>

Thus aneurysm of the left ventricle, being the most common, may be taken as the type of aneurysm affecting the heart walls. Its usual site is at the apex or in the anterior wall immediately above it. The thinned wall of the aneurysm gradually merges into the surrounding myocardium, which may be of normal thickness.

The pouch varies in size and is lined by stretched endocardium—white, opaque and greatly thickened.

The cavity is more or less filled by blood clot. The clot varies in color, density and adherence with its age, the older and deeper layers being laminated, firm and adherent to the heart wall.

Pericardial adhesions are almost constant and often accurately limited to the area of the aneurysm.

In the wall of the aneurysm, microscopically, there may be no trace whatever of muscle fibers, or they may be visible scattered in the abundant connective tissue. At the periphery of the aneurysm the muscle fibers show degenerative changes of varying degree. In most cases the common pathogenesis is thrombosis or endarteritis in the coronary arteries, like that of infarction.<sup>7</sup> Aneurysm is a later formation in such a lesion.

The anterior or descending branch of the left coronary is the one involved when the left apex is affected and may be obstructed by atheroma, fibrinous clot or calcareous deposit. In the large proportion of the cases collected by Hall (in 27 cases) the descending interventricular branch of the left coronary artery was completely

<sup>1</sup> Comment, Bonon, 1757, 4, 26.

<sup>2</sup> Catal. Museum Roy. Coll. Surg., London, 1830, Path. Prep. in Sp. No. 363.

<sup>3</sup> Walter: *Nouv. mém. du Berlin*, 1785.

<sup>4</sup> Thurnam, J.: *Med. Chir. Tr.*, London, 1838, 21, 187.

<sup>5</sup> Legg, J. W.: *Med. Times and Gaz.*, 1883, 2, 199.

<sup>6</sup> Hall, D. G.: *Edinburgh Med. Jour.*, 1903, 14, 322.

<sup>7</sup> Cohnheim: *Virchows Arch. f. path. Anat.*, 1881, 75, 503.



blocked and in 13 it showed atheromatous changes. The right side of the heart may be much smaller relatively, due to the displacement of the septum. The aorta may show atheroma of varying degree. Enlargement of the liver and congestion of the viscera are effects of cardiac failure which are regularly present.

Whenever extensive myocardial changes exist, as indicated by the symptoms and by electrocardiographic observations, or when symptoms of coronary thrombosis are diagnosed, myocardial degeneration and thinning of a portion of the ventricular wall should be suspected. In the main, the symptoms of aneurysm of the heart are not otherwise distinctive from the symptoms of the cardiovascular disease in the course of which the aneurysm develops.

Clinically precordial pain, a feeble apex-beat, weak heart sounds, perhaps gallop rhythm, localized pericardial systolic rub and hypertrophy or dilatation of the left ventricle are some of the symptoms and signs present.

The clinical features that have been considered especially significant in the diagnosis of aneurysmal formation are the severe precordial pain in the region of the apex-beat and the pericardial adhesions localized to this region.

The pain is probably the direct effect of the lesion in the heart wall and pericardium. There is an associated constant point of tenderness on intensive pressure over a localized area of the precordium. This sign persists to the end. The pain may not be typically anginal in character, despite the coronary lesion associated.<sup>8</sup>

The pericardial adhesions localized over the lesion of the myocardium coincide with the appearance of pain and no doubt contribute to its frequency.<sup>9</sup> The adhesions produce a fixity or immobility of the apex, but due to the aneurysmal thinning the apex-beat may not show systolic retraction.<sup>10</sup> This aids in differentiating it from rheumatic pericarditis, in which case the myocardium underneath contracts energetically and draws in the chest wall with every systole. In fact one of the theories of the pathogenesis of aneurysm is that the pericarditis is primary and that traction upon the heart wall by the adhesions is the important etiological factor.<sup>11</sup>

The gallop rhythm is attributed to splitting or duplication of the first sound. This splitting is due to an aortic pressure relatively high for the available myocardial energy, or, in other words, the heart is too weak for the aortic pressure.<sup>12</sup>

<sup>8</sup> Allbutt, C.: Diseases of the Arteries including Angina Pectoris, London, 1915, Ch. 6, vol. 2.

<sup>9</sup> Sternberg, M.: Wien. med. Wchnschr., 1910, 60, 14.

<sup>10</sup> Lutenbacher: Arch. d. mal. du cœur, 1920, 13, 49.

<sup>11</sup> Bureau: Bull. Soc. anat. de Paris, 1892, 6, 736. Rendu: Gaz. d. hôp., Paris, 1887. 60-1318.

<sup>12</sup> Allbutt, C.: Loc. cit., 1, 391. Richet. Congrès de Grenoble, Semaine méd., 1884, 4-517.

Very grave and rapid development of symptoms of cardiac failure without sufficient endocardial or cardiorenal cause may indicate the clinical course of cardiac aneurysm. The distress of the patient seems out of proportion to the physical signs of the illness. Alternation of the pulse is significant.

Roentgen-ray and fluoroscopy are of little help in these cases. The electrocardiogram may show evidence of myocardial disease, but reveals nothing distinctive of aneurysm. In fact no electrocardiographic records have been found reported in the literature of cases of cardiac aneurysm. Extrasystoles occur commonly. Death is sudden in most of the cases.

Aneurysm of the three other chambers of the heart are exceedingly rare and are pathological curiosities. It may affect the left auricle, the interventricular septum, the septum membranacea, the valves, especially the aortic and pulmonic cusps, and finally the coronary arteries.

**Report of Cases.** The following are brief reports of 2 cases of aneurysm of the left ventricle from the time when they came under observation until their fatal issue.

In both cases the severe precordial pain was a prominent feature during the course of the illness; but it was not of the typical sterno-brachial radiating anginal character. Although autopsy findings did show pericardial changes in both instances, clinically this was not diagnosed, and it is difficult to state the exact period at which the pericarditis began.

**CASE I.**—Mitral regurgitation; relative tricuspid regurgitation; cardiac failure; pulsation of the liver; right hydrothorax; electrocardiographic changes; nodal premature beats.

*Autopsy Findings.* Localized pericarditis and aneurysmal thinning and softening near the apex of the left ventricle; calcareous deposits in the wall of the left coronary artery compressing its lumen.

Z. M., an Austrian, aged fifty-one years, was admitted to the hospital May 31, 1920.

His present illness dated back one month before admission, when he began to feel shortness of breath, most marked on exertion, with cough and mucopurulent expectoration at times. Shortly after he was seized with pain over the upper portion of the abdomen, which radiated to the chest and was accompanied by marked dyspnea. The pain abated and then recurred only when walking, was not felt while at rest, and continued with intermittent relief until about May 15, when the dyspnea became more marked.

On admission to the hospital the patient was orthopneic, the lips were somewhat cyanosed and there was prominent pulsation in the veins of the neck.

Physical examination revealed the following:

*Heart.* Diffuse apex-beat was seen and felt best in the sixth interspace to the left of the midclavicular line. No thrills were felt. The left border of the heart percussed out beyond the midclavicular line. The right border could not be obtained. The aortic arch was somewhat wider than normal. At the apex the heart sounds were weak and of poor muscular quality. There was a soft systolic murmur heard best in the sixth interspace and transmitted slightly to the left. There was a systolic murmur heard over the tricuspid area. At the base the heart sounds were hardly audible.

*Arteries.* Pulses were equal and of low tension. There was an occasional premature beat. Arteriosclerotic changes of the radials were present.

*Lungs.* There were sibilant and sonorous rales over both lungs and diminished breathing at the base of the right chest.

*Liver.* The lower border was felt pulsating just above the level of the umbilicus.

*Extremities.* The veins of the legs were slightly distended, but there was no edema.

Diagnosis was made of chronic myocarditis with cardiac decompensation; tricuspid and mitral systolic murmurs; right hydrothorax.

*Clinical Course and Notes.* The temperature was normal during the course of the patient's illness. His pulse was 100, irregular at times, due to premature beats. Within one week it came down to 56 as a result of rest and digitalis, but it gradually returned to between 80 and 100. The respirations were at times 38 per minute, although the usual range was 24 to 30, but almost always labored.

Digitalis in moderately large doses was beneficial for a time; then the signs of decompensation reasserted themselves. The patient complained of distress and dizziness, was restless and slept only at short intervals.

He developed a moderate amount of effusion in the right chest. On July 16 paracentesis was done and 960 cc of dark, straw-colored, turbid fluid were withdrawn.

The general condition of the patient then varied from fair to poor, with weak, slow, irregular pulse and labored respirations.

The liver increased in size and was pulsating.

On August 5 there was marked venous stasis. The face, lips and finger tips were cyanosed. The patient complained of epigastric pain, which may have been due to distension of the liver. Edema of the lower extremities developed.

The following note is recorded on August 28: "The patient has not slept; is restless and irrational. His condition is very poor; his pulse weak and irregular. Respirations are very much labored."

On August 31 he complained of pain in the cardiac region and vomited a large amount of fluid.

The patient died soon after this with sudden cardiac exhaustion four months after the onset of his illness.

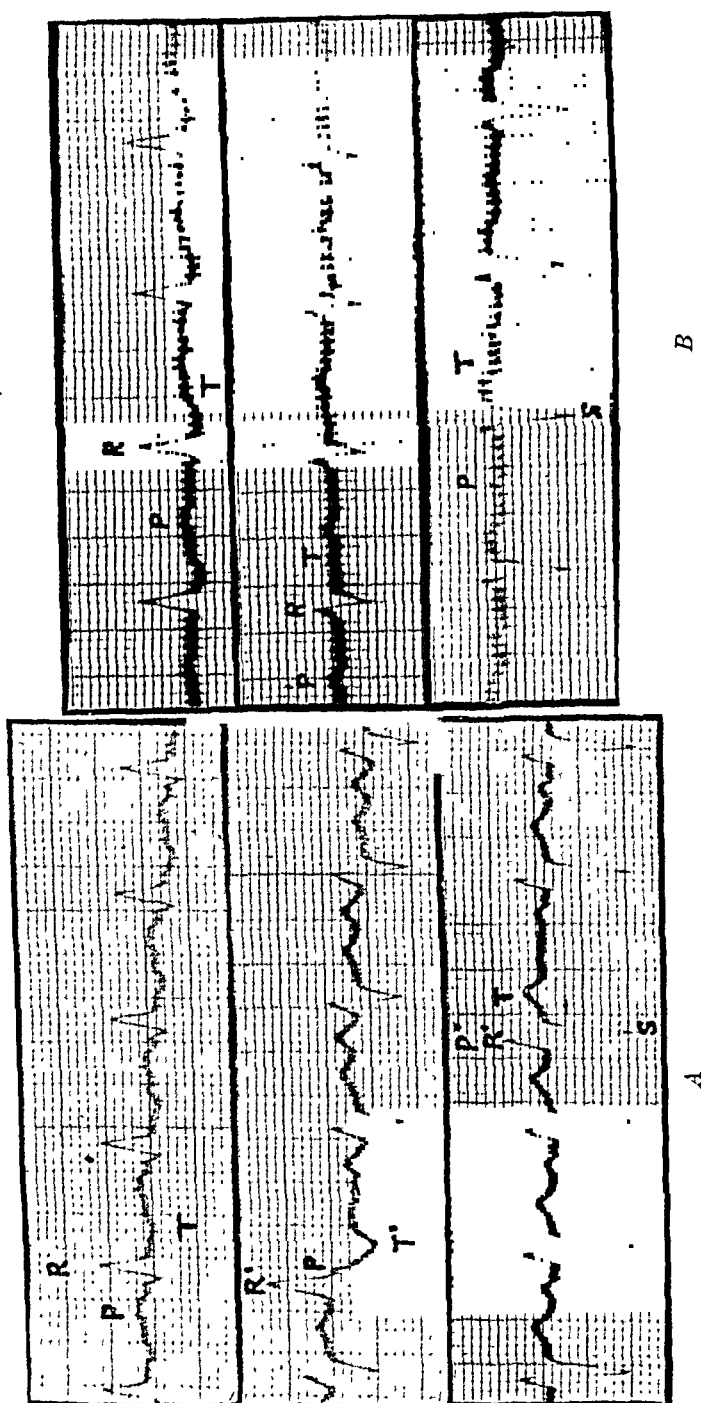


FIG. 1.—A, taken June 22, 1920. The EKG shows low voltage and predominance of the left ventricle. The Q-R-S interval is widened to 0.12 second and thickened in its initial deflection in all three leads. T is inverted in lead I. Lead II shows a bundle extrasystole and lead III a nodal extrasystole, with full compensatory pause in both instances. B, taken August 26, 1920, a few days before the patient died. The voltage is low. T is almost isoelectric in leads II and III and the S-T phase is peculiarly humped. The P-R interval is increased to 0.28 second.

*Laboratory Observations.* The urine showed an abundance of albumin, and at times red blood cells and bile. The blood Wassermann test was negative.

The blood showed slight secondary anemia and slight leukocytosis of between 9200 and 13,600 cells per cu.mm.

The phenolsulphonephthalein test showed functional deficiency of the kidneys, 43 per cent in two hours.

The pleural fluid showed 2300 cells per cu.mm. in the first aspiration, of which 90 per cent were lymphocytes, and 600 cells per cu.mm. in the second of which 60 per cent were lymphocytes. Cultures were sterile.



FIG. 2.—Crayon drawing made directly from the heart of Case I. It shows the aneurysmal thinning at the apex and the fibrosis in the subendocardial tissues. The area of pericarditis was just over the aneurysmal thinning.

*Polygraphic and Electrocardiographic Studies.* Polygraphic studies showed a marked auricular wave in the jugular vein associated with distinct pulsation of the liver of the ventricular type, due to the relative tricuspid regurgitation.

Electrocardiographic studies were made repeatedly during the course of the patient's illness. They showed predominance of the left ventricle. The voltage was low in all three leads and was even lower before the patient died. The *Q-R-S* wave showed widening of 0.12 second and some notching and thickening most evident in lead II. The *T*-wave was inverted in lead I throughout and continued from the *S*-phase without any isoelectric interval. Toward the end the *T*-wave became less distinct and almost isoelectric in leads II and III. There were occasional nodal and bundle extra-

systoles. These changes are illustrated in the figures and explained in their subjoined legends (Fig. 1).

*Autopsy Findings* (Fig. 2). *Heart.* The heart was much enlarged. There was an irregular area of thickening over the pericardium on the anterior surface of the left ventricle. This showed an old patch of pericarditis with an elevated area of subpericardial connective tissue. On section the wall of the left ventricle was very thin. At the auriculoventricular junction it was less than 2 cm. and gradually tapered down to the apex, where the wall was only about 1 mm. in thickness. At the apex of the left ventricle there was an area of softening and marked thinning of the wall about 2 cm. in circumference. Here the muscular tissue was almost completely destroyed; this destruction was more evident the nearer the apex one approached. Large plaques of firm connective tissue were visible throughout the wall, and especially on the septum. The papillary



FIG. 3.—Section at the apex of the heart in Case I, showing the thinning of the wall of the left ventricle and the almost entire absence of muscular tissue (in the left half of the figure).

muscles were firm but showed no new connective tissue. The left ventricle was much dilated; the chordæ tendinæ were well marked. There were no thrombi. The mitral valve admitted three fingers easily. The anterior flap of the mitral showed thickening at the edge. The right ventricle showed distinct hypertrophy and dilatation. The right auricle was very much dilated. The tricuspid valve admitted three fingers. The flaps were normal and the aorta was normal. The pulmonary artery showed slight atheromatous patches.

*Coronaries.* In the main coronaries and the larger branches there were no evidences of thrombosis. At a point 1 cm. from the mouth of the left coronary a plaque of calcareous deposit in the wall compressed the lumen with almost complete mechanical obstruction to the flow of blood. Below this and in the terminating branches the vessel wall was thickened and in places almost obliterated (Fig. 3).

*Lungs.* Both lungs were congested. The pleura over the right lung was thickened and white.

*Liver.* The liver was moderately enlarged and congested.

*Abdominal Viscera.* The abdominal viscera were congested.

*Anatomical Diagnosis.* Aneurysm of the left ventricle; chronic congestion of the viscera; left coronary obstruction 1 cm. below its origin, with calcareous deposit.

CASE II.—Sticking precordial pain and signs of myocardial failure; dyspnea and cyanosis; dilatation of the heart; right hydrothorax; nephritic changes; peculiar pallor associated with myocardial disease; sudden death.

*Autopsy Findings.* Pericardial adhesions; aneurysm of a large part of the left ventricle; left coronary occlusion of the anterior descending branch.

R. N., aged forty-six years was admitted to the hospital June 15, 1920, with dyspnea, pain in the chest, cough and hemoptysis.

The present illness began suddenly one month before the patient's admission with sticking pains in the chest, dyspnea, and marked weakness. She had palpitation, cyanosis of the fingers and cough with rusty expectoration. The sticking pain over the lower sternum was continual.

On admission the patient was pale, dyspneic and severely ill, and she had slight cyanosis of the lips and finger tips and cold, clammy skin. Her face showed a peculiar sallow leaden pallor and an expression of anxiety and suffering.

Physical examination revealed the following:

*Eyes.* The right pupil was larger than the left.

*Heart.* The apex-beat was not seen or felt and there were no thrills. The left border could not be made out. On auscultation the sounds were weak. No murmurs were heard. The aortic second sound was more accentuated than the pulmonic. Digitalis did not improve the quality of the apical sounds. The pulse was regular but scarcely perceptible.

*Lungs.* The lungs showed retraction of the supraclavicular spaces on inspiration; both bases were dull on percussion, with diminished voice and breath sounds.

*Liver.* The liver was felt two fingers below the costal margin and was slightly tender.

*Extremities.* The extremities were edematous.

Diagnosis was made of chronic myocarditis with pleural effusion at the left base.

*Clinical Course and Notes.* On admission the pulse was imperceptible and the respirations were gasping and labored. The patient appeared in grave condition. She complained of a choking sensation, "heaviness" and pain in the epigastric region, pain in the

cardiac region with a sense of oppression in the chest and difficulty in breathing. This condition continued unchanged for days.

The temperature was normal during the course of the patient's illness.

The pulse-rate was fairly even between 80 and 90.

The respirations on admission were between 32 and 38.

After one week's stay at home she was readmitted, with severe sticking pain in the back and in the cardiac region and dyspnea, which were slightly relieved by rest in bed. The pulse was weak and at times imperceptible. She coughed and expectorated a good deal and also vomited at times.

On July 16, twenty-six ounces of blood-tinged fluid were aspirated from the left chest.

After August 1 the pain was mainly in the cardiac region and became more severe and so constant that it is recorded with almost each bedside note. At times the patient was cyanotic, restless and irritable.

On September 15, the chest was again aspirated and 1400 cc of bloody fluid obtained. That day the patient showed marked dyspnea, cold, clammy sweat, and had severe precordial pain. The liver was palpable three fingers' breadth below the costal margin and edema developed on the dorsum of both hands.

The systolic pressure was at times below 120, although it ranged to 145. The diastolic pressure ranged above 45 and up to 90 mm. of mercury. On October 10 it was 145 mm. of mercury systolic and 80 mm. diastolic pressure.

On October 15 the patient became at first faint and then died suddenly, five months after the onset of her illness.

*Roentgen-ray Examination.* Roentgen-ray examination showed marked enlargement of the cardiac shadow to both sides with clouding of the left pulmonary base. The apex was rounded. The heart was rotated parallel to the diaphragm.

*Laboratory Observations.* The urine showed albumin and hyaline and granular casts.

The blood Wassermann test was negative.

The blood showed a moderate degree of secondary anemia and slight leukocytosis of 10,000 cells per cu.mm. at first, and toward the end between 16,800 and 20,800 cells per cu.mm.

The 26 ounces of bloody pleural fluid obtained July 16 contained 260 cells per cu.mm., of which 90 per cent were mononuclears. On August 11 it contained 400 cells per cu.mm., of which 80 per cent were mononuclears.

*Electrocardiographic Studies.* Electrocardiographic examination showed very low voltage and predominance of the left ventricle. The Q-R-S wave showed slight notching, thickening and widening, which became more distinct with the progress of the lesion, reaching a period of 0.12 of a second. The predominance of the left ventricle



also increased during the course of the illness. The  $T$ -wave was at first inverted in lead I and fell directly from the descending or catacrotic arm of  $R$  before the latter had reached the isoelectric

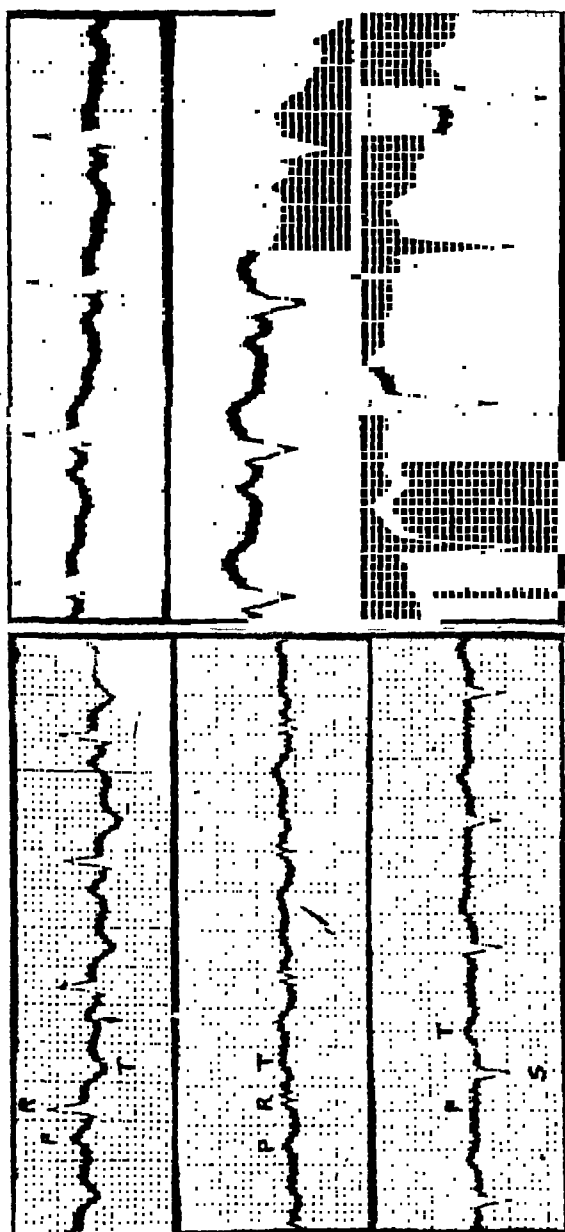


FIG. 4.—A, taken June 23, 1920. The EKG shows low voltage and predominance of the left ventricle. The  $Q$ - $R$ - $S$  wave shows slight notching in lead II and thickening in lead III, and is more than 0.1 second.  $T'$  is inverted in lead I and falls directly from the descending or catacrotic arm of  $R$  from above the isoelectric level. B, taken October 14, 1920. Increased voltage, increased predominance of the left ventricle and increased widening and notching of the  $Q$ - $R$ - $S$  wave. The  $T$ -wave in lead III is more prominent in its upward peak and still continuous with  $S$ .

level. Later it became less prominent and almost isoelectric in lead I. The electrocardiographic studies gave evidence of rapidly progressing myodegenerative changes in the left ventricle (Fig. 4).

*Autopsy Findings* (Fig. 5). *Heart.* The heart was enormous. The pericardial surface was shaggy as a result of old tough adhesions. Viewing the heart from the anterior aspect the left ventricle occupied almost the entire field. The right ventricle occupied a comparatively small area in the right quadrant, triangular in shape and bulging forward. The left ventricle was enormously dilated; the apex wall had been thinned to the thickness of blotting paper. The upper portion of the ventricular musculature was about 2 cm.

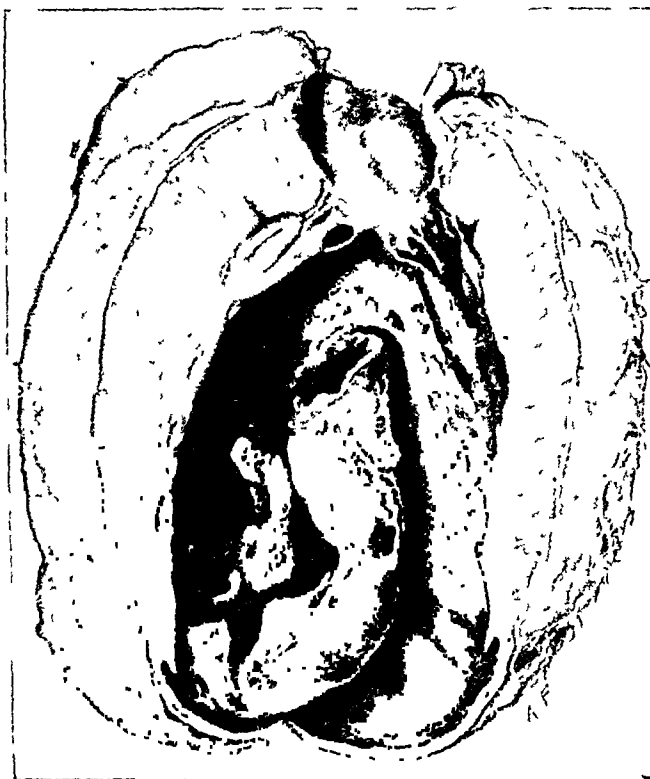


FIG. 5.—Crayon drawing made directly from the heart of Case II. There was occlusion of the descending or anterior branch of the left coronary. The pericardial surface is shaggy, with old adhesions. The left ventricle is enormously dilated. The wall of the aneurysm over the apex is very thin. A large irregular clot almost completely fills the ventricle and is adherent firmly to the septum and less firmly to the wall of the aneurysm. The thrombus undermines the endocardium at the upper edge of the aneurysm.

thick, and toward the apex the thinning was rather abrupt. The endocardium had been undermined by thrombosis which had dissected the wall up to the region where the aneurysm became continuous with the normal muscle. As far as the eye could judge the apical muscle was completely transformed into connective tissue. The ventricular cavity was almost completely occupied by a huge avoid, laminated, hard, white clot. The clot was firmly attached to the septum for almost its entire length and was less firmly adherent to the inner aspect of the ventricular wall. The only part

of the ventricular cavity unoccupied was its upper portion. Irregular masses of fibrinous clot lay loose in the upper part of the ventricle and were an obstacle to the current in the aortic orifice. The mitral valve admitted two fingers easily. There was no thickening. The musculature of the right ventricle was enormously thickened. The cavity was not dilated. The left auricle showed nothing abnormal.

*Coronaries.* The aortic ring showed marked atheroma for a short distance above the semilunar valves. The coronary artery admitted a medium-sized probe for a distance of  $2\frac{1}{2}$  cm. Beyond that the anterior or descending branch of the left coronary was completely occluded. Sections were made of the remainder of its course and it was traced down into the wall of the aneurysm. The corresponding coronary vein was patent. The coronary changes are shown in the illustration (Fig. 6).



FIG. 6.—Section of the descending branch of the left coronary artery in Case II at its termination in the wall of the aneurysm, showing its occlusion by almost hyaline connective tissue. Note also the thinness of the aneurysmal wall.

*Lungs.* The lungs showed old pleural adhesions at both bases.

*Abdominal Viscera.* The abdominal viscera showed venous congestion of moderate degree.

*Anatomical Diagnosis.* Aneurysm of the left ventricle; occlusion of the anterior descending branch of the left coronary artery; cardiac thrombosis; chronic pericarditis with adhesions; hypertrophy of the right ventricle; chronic congestion of the viscera.

*Discussion.* The outstanding features in the 2 cases reported above are: (1) The precordial distress and the prominent circulatory symptoms; (2) myocardial failure, hydrothorax, congestion and enlargement of the liver and congestion of the viscera; (3) electrocardiographic changes, indicating progressive disease in the myocardium; (4) striking similarity in the electrocardiographic records in the 2 cases due to the involvement of the apical portion of the left ventricle in both instances; and (5) coronary obstruction involving the descending branch of the left coronary artery.

The cardiac symptoms developed rapidly in both cases. The onset was sudden and the course precipitant. It may be surmised

that the attack of angina abdominis initiated the symptoms and probably coincided with the pericarditis in the first case, and that the attack of atypical angina pectoris initiated the symptoms and coincided with the coronary closure or pericarditis in the second case.

Kernig called attention to the occurrence of pericarditis within several days following an attack of angina pectoris.<sup>13</sup> Sternberg has shown that the pain is associated with the patch of pericarditis.<sup>14</sup> Josué also says that in most cases of cardiac aneurysm the pain has been absent except for pericardial synechiæ covering the aneurysmal area.<sup>15</sup> The pain in both cases in this report was more constant and continuous than in typical angina pectoris, and in the second case was the dominant feature. Allbutt says that the pain in infarction of the heart is more continuous than in typical angina.<sup>16</sup>

The discrepancy between the apex-beat as seen and the weakness of the sounds is a noteworthy point in the diagnosis of aneurysm of the apex.<sup>17</sup>

The distinctive clinical features that are common to both cases relate to the pericardial adhesions, the myocardial failure and the electrocardiographic changes. Hydrothorax and congestion of the liver and edema developed in both cases.

It has been affirmed that in sudden thrombosis a valuable sign is a moderate degree of leukocytosis. In 2 cases of coronary thrombosis with infarction of the heart recently reported there was a leukocytosis of 21,400 and 33,500, with fever and angina abdominis. The leukocytosis was a perplexing point in the diagnosis.<sup>18</sup> A slight leukocytosis was present in our Case I, 9200 to 13,600 cells per cu.mm. In our Case II, with marked coronary thrombosis, it reached as high as 20,800. It must be remembered that these cases are associated with pericarditis and with anemia, both of which factors somewhat affect the blood count—the anemia relatively and the pericardial inflammation directly.

Changes that take place in electrocardiographic findings within a short interval of time, and without the influence of medication, must necessarily be attributed to functional, nervous, toxic or organic causes. When the changes are so important as widening of the *Q-R-S* wave or variation in the *T*-phase they indicate changes in the myocardium.

There is a striking similarity in the electrocardiographic findings in both cases of aneurysm. This is evident from the figures. The low voltage and the widening of the *Q-R-S*-wave suggest myocardial degeneration. The inversion of the *T* and its variations also evidence progressive changes.

A characteristic alteration takes place in the form of the *T*-wave

<sup>13</sup> Kernig, W.: Berl. klin. Wehnschr., 1905, 42, 10.

<sup>14</sup> Sternberg, M.: Loc. cit.

<sup>15</sup> Josué, O.: Traité de l'artériosclérose, 1909, Paris.

<sup>16</sup> Allbutt, C.: Loc. cit., 2, 463.

<sup>17</sup> Libman, E.: Tr. Assn. Am. Phys., 1919, 34.

<sup>18</sup> Levine, S. A., and Tranter, C. L.: AM. JOUR. MED. SC., 1918, 155, 57.

following experimental ligation of the branches of the left coronary artery in the dog.<sup>19</sup> Immediately following the ligation the *T*-wave becomes more prominent, varying in height with the size of the ligated branch of the left coronary artery. Within twenty-four hours it becomes sharply negative, also varying in size with the artery ligated. After from two to seven days it gradually becomes positive again, first in lead III, then in lead II, then in lead I. After the fourth week the *T*-wave again becomes isoelectric or negative and remains so until death. This change is usually associated with a low voltage *R*-wave. The change of the *T*-wave from the strongly positive peak to a markedly negative one and then a slower return to the positive isoelectric form is so characteristic experimentally that similar changes in the wave in man may reasonably be supposed to be due to similar lesions in the left coronary artery.

It is peculiar that extrasystoles occurred only in Case I, which showed much less involvement than Case II. It is probable that the degenerated condition of the muscle in the second case was no longer a source of excitation of the ventricle, whereas in the first case the degeneration was not so complete and was still progressive at the junction of aneurysm and heart muscle.

Herrick described a case of coronary thrombosis diagnosed clinically in which the descending branch of the left coronary and the large descending branch of the left circumflex were completely obliterated by old thrombi. In this case the electrocardiograms taken forty-one days after the obstructive symptoms showed complete inversion of the *T*-wave in leads I and II. Four and one-half months later the voltage was lower, the *R* was notched and thickened and the *T*-wave was only slightly inverted in lead I and was isoelectric in lead II.<sup>20</sup>

Sternberg discusses the occurrence of pericarditis following attacks of angina pectoris which he calls "pericarditis episteno-cardiaca." It is a notable symptom of this type of myocarditis. He describes the presence of myomalacious foci, either superficial or extending to the surface from large deeper foci, which cause a pericardial exudate. The patch of pericarditis is apparently produced in the same or similar way as the patch of pleurisy over a pulmonary embolism. He divides the clinical picture of these cases into three stages: The first is a period of stenocardial attacks which are the expression of obstruction to the coronary circulation. As a result, myomalacious foci and pericarditis develop in the left ventricle. Then a period follows in which there is a remission of symptoms without pain and with good functional activity of the heart. It is during this stage that the aneurysm may form in the wall of the ventricle. The third stage is the occurrence of sudden death due to heart failure.<sup>21</sup>

<sup>19</sup> Smith, F. M.: Arch. Int. Med., 1918, 22, 8.

<sup>20</sup> Herrick, J. B.: Jour. Am. Med. Assn., 1919, 72, 387.

<sup>21</sup> Sternberg, M.: Loc. cit.

Legg and Samuel West showed that the coronary arteries are not terminal but often anastomosed over the ventricles and the apex.<sup>22</sup> The anastomoses could reestablish circulation in an infarcted area, and, for a time at least, enable the heart to functionate. These findings have been corroborated by many experiments since.<sup>23</sup>

Herrick called attention to the fact that while sudden obstruction of the coronary arteries, as by a thrombus, was very often fatal it was not necessarily so.

There are some cases in which death is delayed for several hours, days or months, or recovery occurs; and some with mild symptoms, for example, a slight precordial pain, ordinarily not recognized, due to obstruction in the smallest branches of the arteries, in which aneurysm of the cardiac wall may develop.<sup>24</sup>

Wooley, in 1917, reported 6 cases of aneurysm of the left ventricle with coronary disease.<sup>25</sup> Hughes and Wilson<sup>26</sup> each reported a case of ruptured aneurysm of the heart at the apex of the left ventricle without any previous symptoms.<sup>27</sup> Recently 2 cases were reported by Lutembacher.<sup>28</sup> One of these showed an aneurysm of the apex of the left ventricle, surrounded by pericardial adhesions, and in the anterior coronary artery there was a small patch of endarteritis partially obstructing its lumen. The second case was associated with precordial pain and muffled sounds and revealed an enormous aneurysm of the left ventricle with pericardial adhesions. The lumen of the anterior branch of the left coronary was obliterated by a fibrinous clot.

**Conclusions and Summary.** 1. Whenever extensive myocardial changes exist, as indicated by the symptoms and by electrocardiographic observations, or when symptoms of coronary thrombosis are diagnosed, myocardial degeneration and thinning of a portion of the ventricular wall should be suspected.

2. In the main the symptoms of aneurysm of the heart are not otherwise distinctive from the symptoms of the cardiovascular disease in the course of which the aneurysm develops.

3. Two cases are presented of aneurysm of the left ventricle with coronary obstruction.

4. Both cases showed electrocardiographic changes indicating progressive disease of the myocardium.

5. The autopsy findings showed aneurysm of the apex and wall of the left ventricle with pericardial adhesions.

6. A brief review of the recent literature on cardiac aneurysm is presented.

<sup>22</sup> Legg, J. W.: *Loc. cit.*

<sup>23</sup> Porter: *Jour. Physiol.*, 1894, 15, 121-138. Hirsch and Spalteholz: *Deutsch. med. Wchnschr.*, 1907, No. 20. Amenoniya: *Virchows Arch. f. path. Anat.*, 1910, 109, 110, 187. Smith, F. M.: *AM. JOUR. MED. SC.*, 1918, 156, 706.

<sup>24</sup> Herrick, J. B.: *Jour. Am. Med. Assn.*, 1912, 59, 2015.

<sup>25</sup> Wooley, P. G.: *Jour. Lab. and Clin. Med.*, 1917, 2, 3, 192, 221.

<sup>26</sup> Wilson: *Lancet*, London, 1919, 2, 199.

<sup>27</sup> Hughes, F. M.: *Lancet*, London, 1914, 1, 533.

<sup>28</sup> *Loc. cit.*

## THE USE OF THE ELECTRIC CAUTERY IN LARYNGEAL TUBERCULOSIS.<sup>1</sup>

By GEORGE B. WOOD, M.D.,

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THERE are few morbid conditions that cause more distress and pain in the final agonies of life than does advanced laryngeal tuberculosis, and there is scarcely another condition in which the physician feels more hopeless, not only in his efforts to prolong life but also in his endeavors to alleviate suffering. There was a time when almost every case of laryngeal tuberculosis, incipient or otherwise, held for the afflicted patient a future to which even his physician could look forward with only dread and misgiving. Of recent years, however, a gradually growing confidence has replaced the pessimism of yesterday, so that today the laryngologist is not necessarily touched by panic when an incipient case of tuberculous involvement of the larynx is first diagnosed. For this, he has to thank not only the modern treatment of general tuberculosis, and we must recognize the efficiency, but also the improvements in local therapy. The local treatment has two purposes: one palliative, applicable especially to advanced and hopeless cases, and the other curative. Both of these, however, overlap in their application. Palliative measures will, at times, permit the swallowing of more food with a consequent improvement in the nutrition of the patient, while, on the other hand, the curative methods are frequently, and almost at the moment of their adoption, attended with distinct lessening of the pain and soreness. In this paper I am dealing only with the question of curing laryngeal tuberculosis. In my experience the application of medicine, such as lactic acid, formalin and other germicides, has little effect upon the progress of the tuberculous disease, though their use is frequently indicated to combat secondary infections. The real curative measures belong to the domain of surgery. Bloody surgery of the tuberculous larynx, though frequently accompanied by very favorable results, has reached the end of its usefulness for the sole reason that the electric cautery will in almost every instance accomplish the same results, with none of its disadvantages, and it does exceedingly more than could ever be hoped for from other surgical procedures. It is undoubtedly the method *par excellence* for the treatment of laryngeal tuberculosis, and its use brings to the surgeon that peculiar sense of elation which he feels when, through his interference, suffering and death have been averted.

Clinically, laryngeal tuberculosis assumes various forms due to the anatomy of the part involved, to the resistance of the individual,

<sup>1</sup> Read before the American College of Surgeons, October 28, 1921.

to the presence of secondary infections and to other modifying circumstances; but the disease itself is essentially a cellular infiltration with the formation of tubercles. This infiltration is avascular, so that the cells in the center of the enlarging tubercle, lacking nutrition, rapidly degenerate under the action of the tuberculous toxins, giving rise to the characteristic caseation. If it were possible to revascularize this tissue a big step would undoubtedly be taken toward the cure of the lesion. Bier recognized this fact when he introduced his method of inducing hyperemia. I believe that the beneficial action of the cautery is due more to the revitalization of the tissues than to the destructive action of the heat.

In 1910 I removed with a cautery snare for diagnostic purposes a portion of a suspicious tonsil from an arrested case of pulmonary tuberculosis. The portion of the tonsil removed showed extensive typical tonsillar tuberculosis. Five days later I removed another portion of this tonsil, including the scar made by the previous cauterization. In this scar there was already a well-developed fibrous tissue, changing the histologic picture, so that now only a single tubercle was found after the examination of numerous sections, and this small tubercle was being rapidly converted into fibrous tissue. This finding led to a series of experiments on guinea-pigs. After experimenting with tubercle bacilli of various degrees of pathogenicity I was finally able to produce localized cutaneous lesions of the abdomen. Some of these lesions I partially excised, as controls, and others I cauterized, not destroying them completely but only making a fairly deep puncture cut through the center with the electric knife. The tubercles partially excised developed without any evidence of even retardation, while those cauterized invariably disappeared. By killing the pigs at various stages a histologic study was made of the healing process.

In three days after the cauterization there developed a distinct zone of inflammatory reaction around the area of destruction. This reaction was manifest by the presence of newly formed bloodvessels, congestion and fibroblasts. In six days the zone of reaction was much more marked and the bloodvessels were larger and more numerous. Also, there was a distinct deposit of fibrous tissue between the epithelioid cells of the tuberculous mass. At this time the tuberculous process beyond the zone of reaction was apparently unaltered, except that it seemed to be decreasing in size. In twenty days a complete fibrous cicatrix had formed throughout the zone of the inflammatory reaction, and though there was still some evidence of the tuberculous disease in the tissue beneath the scar, the epithelioid cells were being rapidly replaced by fibrous tissue throughout the entire tuberculous area. To summarize: An eschar formed by the cauterization is sloughed off by the formation of granulation tissue. The development of the granulation tissue is attended by the formation of new bloodvessels which grow through a previously vascular area. This brings nutrition to the fixed connective-tissue



elements, enabling them to withstand the action of the tubercle toxin, and it is also possible that the epithelioid cells themselves, because of the added nutrition, develop into fibroblasts. The object then of our cauterization of a tuberculous larynx is not so much a destruction as it is a healing of the tubercle, and the great advantage to the patient that the cautery has over bloody surgery is that important organs are not removed or destroyed except by the disease itself. At the present time I believe that all the various clinical types of localized tuberculous lesions, be they infiltrative, ulcerative or of the tumor type, if they are within reach, will be more successfully combated by the cautery than by any other form of treatment, no matter in what part of the throat or larynx they occur.

*Technic.* The object of the cauterization is, as has been stated, the production of an eschar rather than destruction of all the tuberculous tissue, and this fact makes the procedure a comparatively minor affair. The application of the cautery may be done either by direct or indirect laryngoscopy. There are a number of laryngologists who prefer the direct method and some who even use suspension laryngoscopy. In certain cases the direct method can be used with advantage, but the ease with which the cauterization of the larynx can usually be accomplished by the indirect method makes this method the one of choice in the majority of cases. Of course the laryngologist must be trained in the intralaryngeal manipulation of instruments.

Concerning the equipment, it is important that the supply of electricity, whether from battery or from a street current controlled by a rheostat, is of sufficient strength to heat the cautery knives to a white heat almost instantaneously. Also, the platinum point of the knife should be shorter than the usual pattern, in order to prevent burning of the normal mucosa, which is apt to occur from spasmodic closure of the larynx. Three types of knives are necessary: A sharp-pointed knife for puncture; a large, flat knife for searing ulceration; and a small wire loop for treating small infiltrations.

Cauterization of the larynx should always be done under local anesthesia. I prefer the following method: One grain of powdered cocain is placed in a sterile glass and a cotton applicator soaked with sterile water is dipped in the powder. This application is carried into the larynx as far as possible, though in many cases the patient's reflexes will prevent the swab being introduced below the ventricular bands on the first trial. After waiting three minutes a second application is made, using more of the original grain of cocain, and it will be found at this time that the swab can be carried directly to the area to be cauterized. After waiting another three minutes we can generally proceed with the cauterization. However, sometimes a third application is necessary. The swabbing has, in my hands, been much more efficacious in producing anesthesia than the instillation of cocain with the syringe.

Experience alone enables the operator to best judge the amount and character of the burn which he should make in each individual case. As a guiding rule, infiltration and swelling require ignipuncture, while ulcerations should be seared with a broad knife. Tuberculomas, especially those occurring in the interarytenoid space, must be more or less completely destroyed, and here again the larger knife is necessary.

When the epiglottis is involved without ulceration a series of punctures should be made into the swelling, perhaps one-eighth to a quarter of an inch apart. In making these punctures a sharp-pointed, short knife is plunged into the tissue while still cold and then the current is turned on for a moment until there is a surrounding areola of white eschar. If there is ulceration the exposed tissues should be seared with a flat, broad knife. Formerly, and even today by some laryngologists, a badly tuberculous epiglottis calls for immediate removal. I believe, however, that better results can now be obtained with the cautery in almost every instance, though freedom from pain may not be quite as quickly obtained. The very grave risk of a dissemination of tubercle bacilli, however, is avoided and we are able to preserve as much of the epiglottis as has not been absolutely destroyed by ulceration.

The use of the puncture for infiltrations and the broad knife for ulcerations applies to other portions of the upper larynx besides the epiglottis. In the pyriform swellings of the arytenoid, which are so common in laryngeal tuberculosis, ignipuncture is remarkably efficient and the rapid reduction in the swelling is astonishing. Below the level of the arytenoids, however, ignipuncture should not be used, except perhaps in cases attended with marked swelling of the ventricular bands and of the walls of the larynx just above them. Infiltrative growths below this level interfering with the functioning of the cords are usually so intimately connected with these important structures that great care must be exercised in their reduction. The amount of destruction can be more accurately gauged if the tissue is attacked from the surface rather than from a puncture of indeterminate depth. In this region an attempt should be made to remove the exuberant tissue down to the level of the normal structures, and not deeper unless the disease process has already destroyed their contour. When the ventricle of Morgagni is involved, as it frequently is, a broad knife bent sideways should be introduced just below the edge of the false chord. The large tuberculomas which occur in the inner arytenoid region are most efficiently attacked by a broad, large knife. A small wire loop makes the best type of knife for dealing with small tuberculomas on the vocal cords or vocal processes.

I have never seen any very violent reaction following the use of the cautery in the larynx, such as might threaten closure of the larynx from edema, and usually the resulting soreness is only enough to cause a slight discomfort for the first twenty-four to forty-eight

hours. In two cases complete aphonia followed cauterization of the vocal cords; one lasting only for two days and the other for an unknown length of time, as the patient passed out of my hands soon after this happened. I cannot recall, at the present writing, any other untoward result, great or small, following the use of the cautery in the larynx.

The repetition of the cauterization should not be undertaken until the previous one has healed, unless an entirely new area of the larynx needs to be treated. Then a second cauterization may take place within a few days as soon as danger of any reaction has passed. The benefit to be expected from a cauterization cannot be fully determined until probably three or four weeks have elapsed, during which time the slow process of cicatrization is going on. On the other hand it is not uncommon to see the tuberculous ulcer covered with normal epithelium within a week or ten days following the cauterization.

There are, of course, therapeutic measures necessary to a successful handling of laryngeal tuberculosis other than the use of the cautery, as the local lesion is, in the vast majority of cases, associated with pulmonary disease. It is essential that appropriate general treatment be adopted for the control of the pulmonary condition, and this general treatment is an important aid to the local therapy. In many of these cases, however, the cure of the laryngeal condition is so important that sometimes the general therapy has to be modified, so that the patient may be in the hands of a competent specialist. Also as to local measure, we must recognize the importance of vocal rest, the application of various medicines for the control of secondary infections and the relief of pain. Untreated laryngeal tuberculosis usually follows in its course the progress of the pulmonary condition, although frequently it becomes the predominating lesion, developing much more rapidly than the disease in the lungs. On the other hand, I have frequently seen laryngeal lesions heal under the application of the cautery while the pulmonary condition was growing progressively worse. I am so enthusiastic about the use of the cautery in this disease that I believe 90 per cent of incipient cases can be cured and that the benefit obtainable is only limited by our ability to reach all of the diseased structures, provided the patient has enough vitality to produce the necessary reaction for the healing of the burned area.

The use of the electric cautery in the treatment of laryngeal tuberculosis is not a new idea nor am I presenting any special technic. I am simply making an earnest plea for its more widely spread adoption. Any sanatorium not equipped both in its personnel and in its instrumentarium for the cauterization of tuberculous lesions of the upper respiratory tract is not giving its tuberculous patients the utmost of modern medicine, and the laryngologist who fails to avail himself of its advantages is not a proper person to treat this disease.

## PANCREATITIS FOLLOWING MUMPS: REPORT OF A CASE WITH OPERATION.

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(From the Department of Surgery, Yale University.)

THE occurrence of pancreatitis following mumps has been reported many times, although in but one instance was there an autopsy to furnish objective evidence of the disease. In the remainder, clinical findings in the shape of more or less definite symptoms and signs rather than pathological changes in the pancreas provide the data on which the clinical entity is based. The case reported in this paper is added to the series only because at operation the lesion was plainly visible to the operators.

The ordinary text-books of medicine and pediatrics do not mention pancreatitis among the possible complications of mumps, while the larger systems refer to it very briefly. For example, Osler and McCrae in *Modern Medicine*, and the *Nelson Loose-leaf Medicine* in short paragraphs give the symptoms as epigastric pain, vomiting and diarrhea; the former says that it is "not an uncommon" complication, the latter that it is "not common." As many of the cases observed have been in France, it is not surprising that Hutinel and Nobécourt, and also Grancher and Comby, describe the condition slightly more fully and quote some of the original articles.

The possibility of simultaneous disease in these two glands, so similar in structure, has been commented on by many of the older writers, and cases of parotitis accompanied by pancreatitis have been reported. In these the parotitis was not of the epidemic variety but secondary to some other disease. One of the earliest to which a reference was found is in the Latin monograph published by Schmackpeffer, in Germany, in 1817. The patient, a pregnant syphilitic woman, had received quite vigorous mercurial treatment for several months before delivery and had had marked pytalism. She died three days after delivery. For several weeks before, she had had a severe parotitis and abdominal pain attributed to the pregnancy. At autopsy, among a number of pathological findings, intense redness and swelling of the pancreas was recorded. An English clinician who was impressed by the possible connection between disease of the parotids and of the pancreas was Thomas Sewall, who wrote in 1814. He describes an acute swelling of both parotids immediately preceding an illness characterized by intense epigastric pain, nausea and vomiting in a young man who died of what was considered cancer of the pancreas.

In 1836 Mondière, in France, in a series of articles on the pancreas, laid stress on its similarity to the parotid gland and quoted the following two authors, whose original articles have not been obtained: Andral had seen an injected pancreas in a patient who had died of a fever accompanied by a parotitis, and Robouam or Roboica, as variously spelled, some time previously had described a case of parotitis accompanied by pancreatitis. Mondière's information is not detailed or direct.

The next reference to the matter is not found until 1887, when Fabre, in writing a number of papers on his experiences in four epidemics of mumps, described 12 cases which showed marked epigastric tenderness accompanied in 5 instances by diarrhea and in 4 by vomiting. He suggested the possibility that the pancreas might be involved. The author who gave the impetus to the French clinicians in looking for this complication was Cuche (1897). In one epidemic he had 26 cases of mumps, and of these 20, according to his diagnosis, had pancreatitis. Simonin's paper (1903) contained observations on a large number of cases of mumps and an interesting discussion, which is often quoted. Altogether 119 cases have been described in medical literature in which the author claims to have observed a pancreatitis attributed to mumps. The reliability of the diagnoses varies all the way from a questionable one in the case of a girl who was exposed to mumps, and eleven days later had epigastric pain, nausea and vomiting, to a certainty in the case reported by Lemoine and Lapasset, where at autopsy the pancreas and parotids were both carefully examined and found diseased. Not all cases are described in detail, so it is not possible to make an exact statistical study of the time of onset, the age or sex incidence; the stool and urine examinations and the pulse and temperature record are given in only a few instances.

In 56 reports the number of days between the onset of the parotitis and the abdominal symptoms is given. In 28 the interval was four to seven days, but there was one rather doubtful case (Sharp) in which eight weeks elapsed between the two diseases. There were 4 cases in which the time was two weeks, one of them being that of Lemoine and Lapasset, which came to autopsy. Ten times, the interval was less than four days. It is also interesting to note that in five patients in whom symptoms of pancreatitis were fairly marked the parotitis developed after the pancreatitis. These are the observations of four different men, Sharp, Freund, Simonin and Michel, and in the case of the latter the interval was nineteen days. In this respect the complication resembles the orchitis which occasionally precedes mumps. There are also included in the list of 119 cases 4 in which the only indication that the patient had mumps was from the development of symptoms of pancreatitis. These all occurred in families which had recently had or were having mumps and in persons who had not previously had the disease.

Males seem more prone to this complication than females. The sex of the patient was mentioned 99 times— 81 males and 18 females. This may be partly accounted for by the fact that several observers wrote about epidemics among soldiers. When these 62 cases are deducted it leaves the proportion for the civil population 18 to 29 in favor of males. But this figure is too small to use in terms of percentages. Cuche reports 20 cases of pancreatitis among 26 soldiers who had mumps, while Simonin observing 652 cases of mumps over a period of several years in general practice found only 10. Fabre in four different epidemics was only able to count 12 cases which in any way suggested pancreatitis. All of Simonin's cases were also in young men. It seems safe, then, to assume that young men have a greater tendency to develop this complication than girls.

The age incidence is also largely influenced by the groups of soldiers. Although the exact age is not given in every case, 58 of the patients were at least eighteen years of age; 31 are mentioned as children, or the actual age is given as under eighteen. The youngest patient was Finizio's, eleven months old, the oldest Routh's fifty-eight years old, but the next youngest was four and the next oldest twenty-seven. The large majority of the patients, considering the soldiers eighteen to twenty-two years old, are between the ages of eight and twenty-four.

It is difficult to draw any conclusion as to the frequency of pancreatitis in mild or severe attacks of mumps. No author hazards a definite opinion, and from the descriptions it sounded as if it might develop in all degrees of severity. In 12, other complications occurred; orchitis 7 times, involvement of the submaxillaries 3 times, in 1 the sublingual glands were inflamed and in 2 there were signs of meningitis. Phillips reports a case of scarlet fever in which there was a parotitis, abdominal symptoms pointing to the pancreas and a large abdominal mass. It is difficult to decide whether this was a case of mumps or merely a parotitis complicating scarlet fever with an undetermined abdominal complication. It has not been included in any of the figures given.

The duration of abdominal symptoms is usually quite short. In a great many instances the authors imply that the attack lasted only twenty-four to forty-eight hours. The longest duration recorded is twenty-five days, which is quite exceptional, even severe cases lasting only a week. All but the patient of Lemoine and Lapasset, an Algerian soldier, recovered.

All authors in describing the symptoms begin with epigastric pain and tenderness. Many mention the fact that the most sensitive region is usually to the left of the midline and may extend to the left hypochondrium. The pain may be very intense, necessitating the use of morphin. It is usually accompanied by nausea and vomiting. In 40 cases pain was specifically mentioned. Diar-

rhea is given in the systems of medicine as the usual accompaniment of the condition, but in the 30 accounts in which mention was made of the stools 5 were described as normal, 10 as constipated and in only 13 instances was there diarrhea alone. In 2 constipation was followed by diarrhea.

A mass in the epigastrium was felt only 13 times. Zimmerli's description is particularly convincing. In one of his patients the pulsations of the aorta were transmitted through the mass, so that on first examination it was thought the mass pulsated. Its gradual decrease in size was followed from day to day. Jaundice was noted only 3 times.

A slight rise in temperature often accompanies the pancreatitis, though on 4 occasions temperatures as high as 103° and 104° F. are reported. In at least 7 cases there was no rise in temperature. The pulse-rate is seldom mentioned, though 4 cases of definite bradycardia were noted in which the pulse-rate was from 56 to 64 beats per minute even in the presence of an elevation of temperature. In other patients the pulse-rate was as high as 90 to 120.

Urine and stool examinations are rare. In the urine the authors show most interest in the presence of sugar, which was found in only 2 cases in the 23 times that it was sought. Acetone and diacetic acid were found 4 times, in each instance the accompaniment of severe vomiting. In the stools neutral fat was found 6 times. However there were only 7 stool analyses, so that this figure by itself may be misleading. The eleven months' old baby showed a very marked impairment of the power to digest fat (Finizio).

Zimmerli gives the leukocyte count in his sickest patient throughout the course of the disease. There was a primary leukopenia with a relative decrease in lymphocytes (white blood cells, 6800; lymphocytes, 15 per cent), while during convalescence there was still a leukopenia but a relative lymphocytosis of 45 per cent, which, of course, is characteristic of uncomplicated mumps.

In summarizing the observations on these 119 cases one would include the following generalizations: An acute abdominal condition, probably a pancreatitis, is sometimes associated with epidemic parotitis. It occurs more often in boys and young men than in other classes of the population; it usually follows but may precede the parotitis or may be the only manifestation of the disease. It is characterized by intense epigastric pain, often vomiting, occasionally diarrhea or constipation and a slight rise in temperature. A mass may sometimes be felt in the epigastrium. It usually runs a short benign course and has not been shown to affect the internal secretion of the pancreas. The case about to be reported conforms in many respects to this summary, but was more serious in its developments.

**Report of Case.** The patient was an Italian man, aged twenty-three years, whose past and family histories were unimportant. He did not remember having had mumps as a child.

He entered the New Haven Hospital April 11, 1920. About two weeks previously he had had a painful swelling at the angle of the right jaw. His doctor had diagnosed it as mumps, ordered an ice-cap and told the patient he had a little fever. The patient did not suffer much but went to bed. His temperature was normal after four days and he felt better, but on the fifth day he began to have some epigastric pain. This was worse at night, fairly sharp, but was not relieved by cathartics. His temperature began to go up shortly after this, but two days before admission he was able to get up and travel on the train. At the time of entrance he said that he felt very sick and complained of both pain and swelling of the abdomen. There was no history of vomiting.

Physical examination on entrance showed a painless swelling in the right parotid region and a scab on the forehead which he said had come from a boil opened by his doctor a few days before. The patient's color was sallow and he held himself very quietly in bed with knees and thighs flexed. The chief positive findings were in the abdomen. This was distended, with marked fulness in the epigastrium. There was tympany from the xiphoid to 10 cm. above the umbilicus, and then there was a transverse strip of dulness extending across the abdomen, about 6 cm. wide, merging in dulness in the flanks. The tenderness was most marked over this dull area in the middle and to the right but not to the left. There was also muscle spasm and rigidity above the umbilicus. The remainder of the abdomen, as the patient was half-sitting, was dull to percussion and there was a definite fluid wave. The heart and lungs were negative. His temperature was between 100° and 101° F. on the first day. The urine contained no sugar or albumin. The white blood cell count was 17,800, with 80 per cent polymorphonuclear leukocytes.

The patient was obviously suffering from an acute abdominal condition and a tentative diagnosis of pancreatitis was made on the basis of the markedly localized abdominal signs. A laparotomy was performed within a few hours of entrance. A midline incision was made in the epigastrium, releasing a gush of thin purulent fluid of about the consistency and color of tomato soup. This fluid was free in the peritoneal cavity. Six liters were aspirated. The omentum appeared much inflamed, but there was no fat necrosis. Upon exploring the abdomen all organs appeared normal until the pancreas was exposed. This was done by turning up the transverse colon and omentum and by slitting the mesocolon over the pancreas. The capsule was much injected, quite red and very tense, the whole organ being about three times its normal size. Under the capsule there were three small spots from  $\frac{1}{2}$  to  $1\frac{1}{2}$  cm. in diameter, pale in color, which were interpreted as fat necroses in the parenchyma. On opening into one of these no pus was obtained. The impression was that of an acute pancreatitis.



Author.	Date of paper and number of cases.	Sex; age.	Following parotitis, days.	Following other manifestations, days.	Preceding mumps, days.	Symptoms.		Clinical findings.			Urine.	Stool.	Remarks.
						Epigastric pain.	Nausea; vomiting.	Mass.	Temperature.	Pulse.			
Fabro	1887 (12)	...	...	...	...	12+	4+	...	...	...	No albumin	5 diarrheal.	
Zinn	1897 (1)	...	...	...	3	20	...	...	20+	...	...	Loose.	
Cucho	1897 (20)	M. (20) adult	...	...	...	...	...	...	...	...	...	Constipated	
Priestly	1900	M. (25)	7	...	...	+	+	...	+	Brady-	...	Constipated	
Priestly	... (2)	M. (25)	4	...	...	+	+	...	+	cardia	...	Offensive.	
Jacob	1900 (1)	M. (10)	3	...	...	+	+	+	+	...	...	...	Seven days.
Stevens	1901 (1)	M. (10)	3	...	...	4+	?	...	...	...	...	...	
Peck	1902 (4)	M. (10)	...	...	...	+	0	...	Normal	...	...	Diarrhea	
Simonin	1903 (10)	M. (22)	...	...	1	...	0	...	Normal	...	...	...	
Simonin	1903	M. (22)	1	...	...	+	+	...	Normal	...	...	...	
Simonin	1903	M. (22)	5	...	...	+	+	...	Fever	...	...	Constipated	
Simonin	1903	M. (24)	3	...	...	+	+	...	104°	...	...	No diarrheal	Orchitis.
Simonin	1903	M. (21)	4	...	...	+	+	...	103°	...	...	Diarrhea.	
Simonin	1903	M. (21)	5	...	...	+	+	...	Fever	...	...	...	
Simonin	1903	M. (22)	4	...	...	+	+	...	Normal	...	...	...	Submaxillary involved.
Simonin	1903	M. (22)	6	...	...	+	+	...	Fever	...	...	Diarrhea	Orchitis.
Simonin	1903	M. (21)	12	...	...	+	+	...	Fever	...	...	...	Submaxillary involved.
Legendie	1903	Child	3	...	...	+	+	...	...	...	No sugar	...	Icterus.
Galli	1904	Child	14	...	...	+	+	...	...	...	...	...	Autopsy.
Lemoine and Lepasset	1905	M. (19)	...	10	...	+	+	...	...	...	...	...	Abdominal rigidity.
Meynier	1905	(4)	Yes	...	...	?	+	...	...	...	...	...	
Guerin	1905 (2)	...	10	...	...	...	+	+	Low	...	...	Normal	
Guerin	1905	(8)	3-4	...	...	+	+	?	...	...	...	Normal	
Auche	1905 (2)	M. (12)	5	...	...	+	+	?	Low	...	...	Normal	
Auche	1905	M. (9)	2	...	...	+	+	...	...	...	...	Normal	
Ausset	1905	F. (12)	Exposed to mumps, 13	...	...	+	+	...	...	...	...	Diarrhea	
Sarradon	1906	M. adult	3	...	...	+	+	...	100°	100°	...	Diarrhea.	

[illegible]

Author.	Date of paper and number of cases	Sex; age.	Following parotitis, days.	Following other manifestations, days.	Preceding mumps, days.	Symptoms.		Clinical findings.			Urine.	Stool.	Remarks.
						Epigastric pain.	Nausea; vomiting.	Mass.	Temperature.	Pulse.			
Raymond . .	1911-12 (3)	Soldier	6	...	...	+	+	...	...	...	...	Diarrhea	Lymphocytosis.
Raymond . .	...	Soldier	2	...	...	+	+	...	...	...	...	Diarrhea.	
Raymond . .	...	Soldier	Yes	...	...	+	0	...	...	...	...	Normal.	Chill.
Routh . . .	1912	M. (58)	7	...	...	0	+	...	...	...	Sugar; acetone?	...	
Timbal . . .	1913	F. (13)	5	...	...	+	+	...	100°	58	No sugar	Diarrhea and constipation	8 days.
Michel . . .	1913	M.	19	...	...	+	+	...	100°	120	...	...	Operation advised.
Frolich . . .	1913	?	15	...	...	+	+	...	...	...	...	...	Operation for appendicitis 3 days.
Dracinski and Mehlmann .	1914 (3)	M. (14)	4	...	...	+	+	...	...	60	Acetone	Constipation	7 days.
Dracinski and Mehlmann .	1914	F. (10)	Exposed; no parotitis	...	...	+	+	...	Fever	...	Acetone	...	
Dracinski and Mehlmann .	1914	M. (8)	...	Submaxillary, 1	...	+	+	...	Fever	Slow	Acetone	...	Meningitis?
Zimmerli . .	1918 (17)	M. soldiers	?	...	...	+	...	...	Fever	...	...	Thin, fat + Fat, starch	W.b.c., 6800.
Zimmerli . .	(1)	M. (26)	6	Orchitis	...	+	+	...	...	80-93	No sugar	...	
Zimmerli . .	(1)	soldier	...	...	...	+	+	+	...	...	No sugar	...	

Drains were placed to the pancreas and to the flanks and the abdomen closed. The patient's further course in the hospital was complicated by a bronchopneumonia and the development of a pelvic abscess, which was drained four weeks after the original operation. The healing of the upper abdominal incision was, however, uneventful and at no time was there necrosis of tissue about the wound. The patient's temperature was elevated for about a month and his pulse bore a normal relation to it, never falling below 90 and often reaching 110 or 120.

*Streptococcus viridans* was isolated from the peritoneal exudate. A stool examination the day after operation showed no free fat or starch, and on three subsequent occasions was normal. The urine was examined twelve times in twenty-four days, and on one occasion only was there a very slight trace of sugar found. No trypsin was found in the peritoneal exudate. The patient left the hospital in good condition and has not been heard from since.

**Discussion.** This case is of interest for a number of reasons. In the first place it is, as far as has been determined, the only one in which a pancreatitis associated with epidemic parotitis has been seen at operation. With the case of Lemoine and Lapasset, which came to autopsy, it gives visible proof that pancreatitis may follow mumps, and supports the deductions drawn from clinical signs and symptoms in other patients.

The etiology of the condition is also interesting. Haden (1919) in studying mumps in an epidemic among soldiers was able in five instances to isolate an organism from the blood, spinal fluid and lymph glands. This was a Gram-positive diplococcus. He was able to produce with this a late orchitis in rabbits by the local injection of a pure culture. In the case described in this paper *Streptococcus viridans* was found in the peritoneal exudate, but no attempt was made to observe it over any length of time or to associate it with epidemic parotitis experimentally. The healing furuncle on the man's forehead might be suggested as a possible source of infection. It was, however, very superficial and *Streptococcus viridans* is rarely found in such a furuncle. There is a fair possibility that epidemic parotitis may have a streptococcus as its etiological agent, and in that case the peritonitis would be explained as an extension of the metastatic infection in the pancreas. The route from the parotids to the pancreas can only be conjectured.

It is also of interest to observe that during the patient's two months' stay in the hospital there were no sequelæ that could be traced to impairment of pancreatic function. There was at no time interference with pancreatic digestion in the intestine as indicated by the stool, or disturbance of carbohydrate metabolism as revealed by urine examination. An article by Harris (1899) should be mentioned in this connection. He reports a case of

diabetes mellitus in a man whose only previous illness was mumps three years previously. No proof is offered, but the suggestion is made that the inflammation of this organ had led to impairment of its function of internal secretion. There are other cases on record in which extensive injury has been done to the pancreas with no apparent effect on its function. A notable example of this is reported by Miller (1916). A practically normal sugar tolerance was found in his patient in whom the pancreas had sloughed away in very great part three years previously. This case was not associated with mumps.

The absence of fat necrosis in the other abdominal organs, and the fact that there was apparently no drainage of pancreatic juice after the operation, show that the inflammation, whatever its etiology, was not very destructive in character. The few small spots of fat necrosis did not apparently enlarge and the capsule was a sufficient barrier to prevent the pancreatic juice from escaping.

A word may be said on the subject of bradycardia of mumps on account of its supposed relationship to pancreatitis. By the time this patient had come to the hospital his pulse was that of an acute peritonitis, so that if he had had a slow pulse it must have been before he came under our observation. Raymond who has attributed the bradycardia of mumps to the pressure of the swollen pancreas on the solar plexus might welcome this evidence that the pancreas really does swell; but so much more reasonable is the explanation of Roux, that the change in rate is due to a toxic rather than a mechanical effect, that the fact of the actual increase in size deserves only passing comment in this connection.

Practically all of the observers who have described pancreatitis following mumps lay emphasis on its mild character, though a number of them tell of alarming symptoms at the outset. Michel (1913), for example, saw a man whom he considered *in extremis*. The patient had been vomiting a great deal, had a small, rapid pulse and a board-like abdomen, but a laparotomy was impossible because of his distance from a hospital. He recovered, though slowly, as in his case the parotitis followed the pancreatitis. The Algerian soldier of Lemoine and Lapasset is the only one among the 119 cases with a fatal termination. That this complication may be serious is seen in the present instance, in which a true peritonitis developed in connection with an acute pancreatitis and in which the operative procedure was clearly justified. Barker, Robson, Deaver, Erdmann and Bornhaupt all advise early operation and thorough drainage in the customary type of acute hemorrhagic pancreatitis, and although the inflammation of this organ in mumps may usually be of little importance, it must not be discounted when serious, merely because of this association. This might be construed as advice to operate in all cases of mumps pancreatitis, which

in view of the usual prognoses would be rather radical. In the case reported the blood picture showed definite evidence of something more than an uncomplicated mumps pancreatitis.

**Conclusions.** 1. A case of epidemic parotitis was followed by abdominal symptoms diagnosed as acute pancreatitis and an operation showed a swollen, acutely inflamed pancreas with a large quantity of peritoneal exudate.

2. The organism isolated from the peritoneal exudate was the *Streptococcus viridans*.

3. Pancreatitis is an occasional and usually unimportant complication of epidemic parotitis. Rarely it becomes fulminating and requires operative treatment.

In concluding, the author wishes to thank Dr. S. C. Harvey, who operated on the patient, for the privilege of reporting the case.

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## EPIDEMIC ENCEPHALITIS: CLINICAL OBSERVATIONS IN SEVENTY-EIGHT CASES, WITH SPECIAL REFERENCE TO END RESULTS.

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DURING the encephalitis epidemic of the winter of 1919-1920, and subsequent endemic period, the author had the opportunity of studying a considerable number of cases, and has been able in most instances to keep track of them for periods varying from a few months to a year and a half or even longer.

A diagnosis of epidemic encephalitis was made 78 times, the date of onset of the disease being as follows: In 1919: June 1, September 1, October 2, November 7, December 6. In 1920: January 15, February 6, March 8, April 3, May 5, June 2, July 4, August 1, September 3, November 2, December 2. In 1921: January 4, February 2, March 4. It will be seen that the curve of seasonal incidence of the epidemic rose in the late fall, reached its maximum in midwinter and declined during the spring.

Approximately one-third of these patients were, for a variable period of time, directly under the care of the author. The balance were seen in consultation; some reëxamined months after the onset, the end-results in the rest being reported through the courtesy and coöperation of their attending physicians.

The end-results naturally fall into three groups: (1) Complete recovery; (2) incomplete recovery; (3) death.

Group I. This includes all cases recovering from the infection and showing no symptoms or sequelæ after several months.

Nine cases cannot be considered in this group, as there has been no late examination of 4 patients (known to be alive), and 5 more are of too recent development to be included, although they will in all probability recover and be in either Group I or Group II.

Of the remaining 69 cases, 19, or 27.5 per cent, have completely recovered.

Group II. Of the known incomplete recoveries there are 30 out of 69 cases, or 43.5 per cent.

Although diplopia is such a frequent early symptom, no strabismus was found in any of the cases as a late effect, while a dilated and inactive or sluggish pupil was present in 3 patients after five, nine and ten months respectively. This is in accord with the observation of Woods<sup>1</sup> and others that the return to normal of the intrinsic eye muscles is slower than that of the extrinsic muscles.

Mental symptoms persisted in 1 case after nine months, in a

<sup>1</sup> Cases of Lethargic Encephalitis, Arch. Ophthalm., 1920, 48, 536.



second after eleven months, and a third case, seen nearly a year ago, has recently been sent to a hospital for the insane. Still another patient, not included in the series, was seen at the State Hospital for the Insane at Medical Lake, Washington. This patient, a girl, aged eighteen years, had a right hemiplegia with athetosis and marked dementia as the result of a typical encephalitis occurring eighteen months previously.

Epileptiform convulsions persisted in 4 patients after five, eleven, twelve and fourteen months. Unilateral, clonic, rhythmic spasm of the muscles of mastication was present in one case after eighteen months and a marked intention tremor of the facial muscles of one side persisted in another patient after seven months.

In 1 patient tremor, asthenia and a general slowing of movement remained after six months. In another case, a male, aged forty years, dizziness, weakness of the left face, widening of the left palpebral fissure, slowness of movement and intention tremor of the right hand were present ten months after the onset of the infection.

A male patient, aged thirty-six years, developed the paralysis agitans syndrome at the time of a relapse, the symptoms persisting, unabated, fifteen months later. A second typical picture of paralysis agitans was observed in a male, aged thirty-eight years, thirteen months after his encephalitis infection.

A man after eight months had neuralgic pain in one fifth nerve distribution, Romberg sign, lost abdominal reflexes and loss of pain and temperature sense over the right upper and lower extremities and right half of the trunk.

Another interesting end-result was noted in a man, aged fifty years, who after one year had marked asthenia, excessive salivary secretion, weakness of the right face and intention tremors of the tongue, the lips and the fingers.

Spastic diplegia was present in 2 patients as an end-result, and another instance of permanent motor paralysis (hemiplegia) has already been referred to in connection with persistent mental symptoms.

Bulbar crises were observed in a child as late as eleven months after the onset of the infection.

In addition to the sequelæ described above, several adults presented marked neurasthenoid symptoms with insomnia and periods of depression persisting for a long time after the disappearance of the organic symptoms.

Group III. There were 19 deaths in the entire series of 78 cases, giving a mortality of 24 per cent.

The average duration of the disease at the time of death was four weeks. The earliest occurred on the eighth day and the latest at four months.

One fact stands out clearly that children and young adults resisted the infection much better than those of middle life or old age. Thus,

13 of the 19 deaths were in patients over forty and only 1 death occurred in a patient under twenty years of age.

Although 75.6 per cent of the cases did not succumb to the infection, it is rather striking that nearly half of this number presented symptoms directly traceable to the disease after many months had elapsed, and it is certain that a considerable proportion of these symptoms are of a permanent character.

A favorable or unfavorable prognosis could not be made from the character or severity of the initial symptoms, as sometimes a case with mild symptoms at the onset would have a severe relapse and a fatal termination, while other cases, apparently unfavorable at the beginning, would make a good recovery. This was true even when bulbar, severe choreopsychotic or meningomyelitic symptoms were present. In general it may be said that simple, uncomplicated ocular cases gave the best prognosis, although 1 such case had a severe relapse with subsequent bulbar and spinal symptoms.

**Association with Pregnancy.** Two of the patients were pregnant. One woman, seven months' pregnant when she contracted the infection, died shortly after the symptoms of encephalitis developed. The other patient, in the earlier months of pregnancy, recovered and was subsequently delivered of a healthy child at term by Caesarean section. Her physician, Dr. Bumgarner, of Harrington, Wash., recently reported that both mother and child are still living, the mother having spastic diplegia as a result of the infection.

**Age of Occurrence.** That epidemic encephalitis may occur at any age is shown by the following figures: Five patients in the series contracted the disease in the first decade; 11 in the second; 14 in the third; 10 in the fourth; 18 in the fifth; 12 in the sixth; 5 in the seventh; 2 in the eighth; and 1 in the ninth. The youngest patient was sixteen months and the oldest eighty-two years.

**Relation to Influenza.** The author has no definite figures to offer regarding the association of the two infections. The number of the patients with encephalitis who had a prior attack of influenza was probably no greater than the average incidence of influenza in the community. On the other hand, it was observed that in a considerable proportion of the cases there was a history of a mild nasopharyngeal infection at the onset of the encephalitis unaccompanied by the characteristic grippal fever, backache and prostration, variously described as mild tonsillitis, cold, sore-throat, cold in the head, etc. In still another group of patients there was an entire absence of anything suggesting inflammation of the nasopharyngeal mucosa.

It may be of interest to note here that only 1 case of true acute anterior poliomyelitis came to the author's attention during the entire period of the encephalitis epidemic.

**Laboratory Findings.** When the blood was examined early in the course of the infection a moderate leukocytosis was the rule, the

average for the series being 11,775. The highest count was 22,000, dropping rapidly to 11,400. About one-third of the cases examined gave no change in the blood picture.

The author's experience with regard to examination of the cerebrospinal fluid accords with that of other observers. When examined early in the course of the disease there was usually some change, such as an increased cell count, an increase in the globulin content and increased pressure. To this there were exceptions, such as a normal fluid even when the examinations had been made within the first few days of the disease and marked changes occurring some months after the onset.

As a rule the cell count did not exceed 10 per cm. In a few it was 30 to 40 per cm., in others 100, and in 1 case during a marked relapse two months after the onset the cell count on two occasions was 250 and 300 respectively. These counts were made by competent laboratory workers, and are so exceptional as to be worthy of special mention.

The spinal fluid in a patient seen in consultation with Dr. Bird was most unusual. It was obtained with difficulty and resembled mucus in appearance and consistency. When examined under the microscope no cells nor bacteria were found, and all cultures were negative. The fluid was not of a yellowish color, as in Froin's syndrome.

The Lange colloidal-gold test was not made in a sufficient number of cases to warrant any conclusions' being drawn.

**Temperature.** Usually there was at least a slight febrile curve, 100°, 101° or 102°F. This usually appeared at the onset, but sometimes would be delayed for one or two weeks. Several patients had a temperature reaching 104°F. and others presented no temperature change at all, although in some instances there may have been a slight temperature rise before they were seen by the attending physician. One unmistakable case of encephalitis with diplopia and optic neuritis was in the hospital as a pupil nurse when she contracted the disease, and her temperature was carefully watched from the onset, but at no time did it deviate from the normal. Another patient had a temperature curve resembling that of typhoid fever both as to course and duration.

**Symptoms.** So much has been written of the various symptoms and clinical types of encephalitis that we will not take up much time with a discussion of this phase of the subject, feeling strongly that the disease should be regarded broadly as a generalized infection of the central nervous system and that something is lost when we attempt to separate it into special clinical types.

A few points, however, appear worthy of mention: Of general symptoms fever was the most common, headache next in frequency (50 per cent), vertigo and vomiting following in equal proportion (27.5 per cent).

Of the special symptoms, those referable to the eye were by far the most frequent, something over 80 per cent of all cases examined presenting some ocular symptom or combination of symptoms. Of these, diplopia, ptosis, pupillary inequality and nystagmus occurred in frequency in the order named. Optic neuritis was found in only 3 patients, although a fundus examination was made in almost every case. Transient hemianopsia was complained of by 2 patients.

Next in order of frequency were either delirium or confusion (46.25 per cent) and some manifestation of increased motor irritability (45 per cent). Muscular twitching, tremors, choreiform movements, convulsions and athetosis appeared in the order named. Hiccough was present in a small percentage of cases.

The author was unable to obtain any history of lethargy in several cases, and considers it of less importance clinically than mental confusion, cranial nerve involvement or increased muscular irritability. Euphoria was not infrequently observed, when present it usually preceded the lethargy and was generally of comparatively short duration. The author's observations regarding euphoria differ from those of Kirby and Davis<sup>2</sup> who frequently noted euphoria after a lethargic or delirious phase and not as an early symptom.

Radicular pains were present in 36.2 per cent of the patients and were often described by them as being electric or shock-like in character. Paresthesias were not infrequent, but actual sensory diminution or loss was rare.

Involvement of the facial muscles of expression was noted in 27.5 per cent of cases, usually unilateral, while disturbance of either the sensory or motor division of the fifth nerve was comparatively rare, seen only in four or five patients.

Bulbar symptoms were present in 11 patients.

Some abnormality of the abdominal reflexes occurred with sufficient frequency as to render this, a most important diagnostic symptom. Complete absence of all abdominal reflexes was noted in 18 patients, in 3 the reflexes were absent on one side and diminished on the opposite side, in 1 case they were absent on one side and normal on the other side, in 3 instances they were diminished on one side and normal on the other and in 1 instance markedly diminished on both sides. The author regrets that he has no accurate figures to offer relative to this symptom, owing to the fact that several of the cases were not seen until some time after the onset of the infection, and in some instances the patients were ambulatory and not completely disrobed for examination. Therefore the percentage of cases (33 per cent) with demonstrable changes in the abdominal reflexes is, in all probability, much lower than the actual incidence of occurrence.

<sup>2</sup> Psychiatric Aspects of Epidemic Encephalitis, Arch. Neurol., and Psych., 1921, 5, 491.

Nine of the series had pronounced spinal symptoms, 1 case was clinically an acute myelitis without any organic cerebral symptoms, but cleared up rapidly and completely.

Thyroiditis developed during convalescence in 1 patient and was the only instance of thyroid involvement in the series.

**Mental Disturbance.** In the cases studied there was no pathognomonic nor diagnostic mental picture. Like the physical symptoms the mental symptoms were protean in their manifestations, yet could be classified either in the delirium, confusion, stupor group or as dementia. The exaltation and depression did not present the characteristic features of the manic-depressive psychosis, but were similar to the mental state common to intoxications. The confusion differed in no sense from that common in infection—exhaustion psychoses and the delirium, while at times superficially resembling mania, always presented some disorientation and amnesia. The same may be said of the so-called lethargy or stupor, although, as pointed out by Jones and Raphael,<sup>3</sup> the lethargic state to which they apply the term “substuporous stage” was strongly suggestive of the disorder and of all the various psychiatric phases of the disease was the most characteristic. When quantitative mental change appeared in the acute stage it suggested paresis. When occurring as an end-result it was undistinguishable from any terminal dementia. In one case the mental picture suggested the mental enfeeblement of an old dementia precox.

**Epileptiform Attacks.** That epileptiform attacks, either Jacksonian or general, may occur as the sole neurologic manifestation of epidemic encephalitis appears not only possible but probable. During the height of the epidemic the author, on several occasions, was called upon to examine cases with convulsive attacks as the chief or only neurologic symptom. These cases presented no evidence of idiopathic epilepsy, brain tumor, syphilis, kidney or cardiovascular disease.

In certain instances, epileptiform attacks were the chief manifestation, but were associated with other slight but unmistakable symptoms of encephalitis, so there was no difficulty in arriving at a diagnosis. These cases constitute what may be termed an intermediate group, pointing the way toward the acceptance of a group presenting only epileptiform attacks clinically.

The following cases illustrate the intermediate group:

**CASE I.**—F. W. K., male, white, aged forty-eight years, manufacturer and fruit-grower. This patient, while shaving, had his right arm suddenly draw up and his head turn to the left. He did not lose consciousness and in a few minutes was apparently all right. Following this he had considerable headache and occasional vomit-

\* The Psychiatric Features of so-called Lethargic Encephalitis, Arch. Neurol. and Psych., 1921, 5, 150.

ing, and within the next two or three weeks developed neuralgia-like pains in the upper and lower jaws on the left side and occasionally sensations, which he described as "electric shocks," on the left side of his chest. Upon examination he presented slight Romberg and unequal knee-jerks, the right being somewhat exaggerated. On testing for Babinski the left great toe responded normally in flexion, but the right great toe made no response in either direction.

The eye-grounds were normal; urine normal and spinal-fluid examination (two weeks after the onset), including Wassermann and colloidal-gold test, was negative. Heart and blood-pressure normal. Although complaining of being readily fatigued and of stiffness in his neck, he had no further symptoms, and in a few weeks was apparently well and conducting his business as usual.

CASE II.—I. D. L., male, white, aged seven years. Referred by Dr. H. E. Wheeler. This boy, just prior to Christmas, 1919, developed a spasm of the muscles of the left side of the face without loss of consciousness. Later he had general convulsions with unconsciousness. Twitching of the muscles of the left face recurred at frequent intervals.

There was some fever at the onset when examined, January 19, 1921. In addition to the muscular twitching and convulsive attacks there was definite weakness of the external rectus muscle of the left eye. No other neurologic symptoms were present.

There was a leukocytosis of 11,000. The cerebrospinal fluid, including a Wassermann test, was negative, also the urine. An ophthalmological examination revealed no optic neuritis. This patient continued to have convulsions, diminishing in frequency, as late as November, 1920.

To avoid multiplying histories we will limit the reports of convulsive seizures unaccompanied by other neurologic symptoms to two cases.

CASE III.—P. K., pharmacist, aged forty-two years. Referred by Dr. S. B. Hopkins. This patient had a series of convulsions commencing in December, 1918, and continued until the spring of 1920, when they ceased. The attacks were characterized by unconsciousness, generalized convulsions, and were followed by transient amnesia. He had bitten his tongue but never voided urine during an attack. He stated that at times he would feel as if his eye were crossed, yet he had no diplopia and no objective eye symptoms.

He was married and had one healthy child. There was no history of prior illness except pneumonia five years ago and an occasional cold. The family history was negative as to epilepsy or other nervous or mental disease.

A careful neurological examination was entirely negative, and Dr. Hopkins reported nothing abnormal upon ophthalmological examination. The urine was negative upon repeated examinations. The cerebrospinal fluid gave a cell count of 25 per cm., no increase in globulin, colloidal-gold reaction 0000000000, Wassermann negative in dilutions of 0.3, 0.5 and 1 cc.

CASE IV.—W. E., merchant, aged forty-two years, referred by Dr. A. A. Mathews. This patient complained of headache, general weakness and convulsive attacks. The first attack occurred in September, 1919. Since then the attacks have recurred at intervals varying from one or two a week to one in two or three months. They also varied as to type. The first occurred while he was walking along the street and consisted in a feeling as if the whole body was asleep, which lasted for only a few seconds. Some of the spells have been characterized by loss of consciousness, falling, muscular rigidity and spasm. Other attacks have consisted of a drawing up of the right arm and rigidity of the right leg with clonic spasm of the arm and no disturbance of consciousness.

He had considerable intermittent headache, occasional vomiting and slight dizziness.

Careful neurological examination revealed nothing definite. There was possibly a slight weakness of the right face, but this was open to question. A blood Wassermann was negative and a spinal-fluid examination was negative as to Wassermann and colloidal-gold test, showing no increase in globulin. There were 27 cells per cm. The urine had a slight trace of albumin on one test and at another time contained a few hyaline casts.

Heart sounds were normal; blood-pressure normal. Dr. O. M. Rott reported no evidence of optic neuritis nor other fundus abnormality.

This patient was kept under observation for some time and since then has been kept track of through correspondence, and reports gradual improvement with disappearance of the headache and diminished frequency of the attacks.

While anticipating and fully realizing the possible criticism and objections to the diagnosis in the cases cited the author holds that the occurrence of these several clinical pictures, together with other similar ones during an epidemic of encephalitis, makes for the consideration if not for the acceptance of his hypothesis.

**Relapses.** In looking over my cases histories with reference to relapses I find that they were of frequent occurrence, bore no definite relation to the severity of the initial symptoms, could occur when the patient had apparently recovered, and many months after the onset. Further, it was not unexpected to note that many of the relapses could be directly traced to overexertion or fatigue of the patient.

CASE V.—A. L. McC., male, aged forty-nine years, referred by Dr. Bertling. Developed the characteristic root pains during the latter part of April, 1919, rapidly followed by diplopia, fever, vertigo, twitching of the facial muscles, somnolence and mental confusion. He had apparently recovered and took a long automobile ride on or about July 3, 1919. When seen on July 7 he was in a katatonic state, lying with the extremities flexed. If an arm was raised he would allow it to remain in that position indefinitely. His speech resembled that of paralysis agitans, the face was mask-like and he had a passive tremor of the hands. The abdominal reflexes were lost. The spinal fluid showed the characteristic findings and was under increased pressure. The Wassermann was negative.

CASE VI.—G. H., female, aged twenty years, nurse, referred by Dr. Francis Rose. Onset August 1, 1920, with headache and nausea. When examined one week later she presented no symptoms of involvement of the nervous system except partial ptosis of the right upper lid. She acted as if overstimulated mentally, had an abnormally slow pulse (47, normal pulse 80). Leukocytos, 8600. Spinal fluid under increased pressure with 3 to 5 cells per cm. This patient made an apparently rapid recovery and was up and about the hospital by the end of the month. She then had a relapse, developed marked headache, vertigo and optic neuritis, the latter persisting until the latter part of October.

CASE VII.—F. F., female, aged twenty years, referred by Dr. Brazeau. Onset about January 15, 1920, with headache, blurring of vision and marked inequality of pupils associated with what she described as a cold in her head. She promptly recovered except for intermittent headaches, which she believed due to eye-strain, and for which she consulted Dr. Brazeau in May. When examined May 27 the left pupil was widely dilated and reacted very sluggishly to light and accommodation. There was widening of the left palpebral fissure, slight weakness of the lower left face and the tongue protruded slightly to the left. She had some thickness at times in her speech. The following day she developed dizziness and pathological drowsiness, falling asleep in the theater.

CASE VIII.—K. C., female, teacher, aged twenty-four years. Just before Christmas, 1918, she developed a condition diagnosed as tonsillitis. At this time she saw double. After three days the so-called tonsillitis and the diplopia disappeared and she resumed teaching. During the last week in January, 1919, she relapsed, and when examined February 7 had unequal pupils, weakness of the right external rectus, drooping of the right lid, smoothing out of the right face, general paresis of the extremities and back muscles



with double Babinski. Speech was almost indistinguishable. She was confused mentally. The spinal fluid gave 6 cells per cm. and increased globulin. The leukocytes were 14,200. Later she made complete recovery and is now teaching.

Other patients in the series had relapses, but the above are fairly illustrative.

**Pathology.** No unusual pathological findings were observed except in one instance, a case autopsied by Dr. Frederick Epplen. Besides the usual brain picture of encephalitis there was considerable exudate on the membranes over the vertex, involving both hemispheres. In an area more or less circumscribed by adhesions between the leptomeninges and the dura the meninges were putty-like in color and consistency, in striking contrast to the usual postmortem appearance.

**Diagnostic Difficulties.** Being so far removed from the centers of scientific supremacy and intellectual infallibility the author unblushingly admits that in his study of encephalitis he has been frequently perplexed and has made mistakes.

The first case of encephalitis that came to his attention was diagnosed as brain tumor and an unfavorable prognosis given; the patient, a child, thereupon made a prompt recovery, much to the author's personal pleasure but professional chagrin. In another case presenting a hemiparesis and marked somnolence, without optic neuritis or any considerable headache, the diagnosis was in doubt until the autopsy, when a small glioma was found in the right frontal lobe.

Another patient presented clinically a typical picture of epidemic encephalitis and for a time was so considered, but subsequently proved to be a case of veronal poisoning. The difficulty of differentiating between veronal poisoning and epidemic encephalitis, unless a history of the taking of the drug could be obtained, has been emphasized by other writers.

Probably the greatest difficulty experienced was in differentiating between encephalitis of the apoplectiform type and true apoplexy, and between convulsive seizures due to encephalitis and those resulting from other causes. At times it was only after repeated laboratory examinations or watching the development and course of the condition that a positive diagnosis could be determined.

Like Gwyn<sup>4</sup> the author would emphasize the value of the history of the onset and course of the disease as diagnostic helps.

**Treatment.** The author has nothing new to offer with regard to the treatment of epidemic encephalitis.

When seen early the patient was kept absolutely in bed, even though the symptoms were slight. All visitors, excitement, loud noises and bright lights were avoided as far as possible. Spinal

<sup>4</sup> The Epidemiology and Diagnosis of Encephalitis Lethargica, Canadian Med. Assn. Jour., 1921, 40, 169.

punctures with withdrawal of 20 to 30 cc of fluid were used freely as a therapeutic measure and was frequently followed by marked amelioration of the symptoms. This procedure was especially valuable when the fluid was under increased pressure and the cell count high, as in the case cited with 250 to 300 cells per cm. In not every case, unfortunately, were good results obtained by this method.

Hexamethylamine was given routinely, but without benefit as far as could be determined. Opium, despite the caution of some writers, was used freely in the form of the deodorized tincture whenever there was marked mental restlessness or delirium.

Luminal proved most efficient in controlling the severer forms of muscular excitation, being superior to hyoscine or to the combination of hyoscine and morphine.

In 2 instances the attending physician gave a full dose of arsphenamine intravenously. In 1 case of the paralysis agitans type the injection was given several weeks after the onset, and was said to have had a favorable influence on the disease. In the second case the arsphenamine was given in the early, acute stage of the infection, the case terminating fatally within forty-eight hours later.

The author feels that there is no indication nor justification for the administration of arsenic preparations in epidemic encephalitis.

Autoserotherapy, advocated by Brill, and injections of turpentine as used by Pic and Netter were not tried.

**Conclusions.** Approximately one-fourth of the cases of epidemic encephalitis seen by the author terminated fatally. Of the remaining three-fourths, approximately 61 per cent were left with persistent or permanent sequelæ.

Relapses were of frequent occurrence, bore no definite relation to the severity of the initial symptoms and could occur several months after apparent recovery.

Prognosis could not be determined from the character and intensity of the initial symptoms, as a patient with mild symptoms at the onset could have a fatal relapse, and sometimes cases with severe and massive initial symptoms recovered.

Epidemic encephalitis is not infrequently associated at the onset with symptoms of nasopharyngeal infection, but bears no direct relation to true influenza.

Age bears a definite relation to mortality, children and young adults standing the infection much better than those of middle life or old age.

Change in the abdominal reflexes is a frequent and important symptom in epidemic encephalitis, probably not hitherto sufficiently emphasized.

Epileptiform attacks may occur as the sole manifestation of the infection.

Rest, quiet and care in preventing too early activity on the part of the patient are essential in the treatment of epidemic encephalitis.

## FEBRILE STAGES IN CHRONIC NEPHRITIS: THEIR SIGNIFICANCE AS OBSERVED BY FUNCTIONAL RENAL TESTS.

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BRIGHT<sup>1</sup> in his early description of nephritis recognized the part acute diseases played in that disease and comments as follows: "A child or an adult if affected with scarlatina or some other acute disease . . . awakens in the morning with his face swollen or his ankles puffy or his hands edematous." Other possible etiologic factors, as intemperance, suppressed catamenia and "exertion in childish plays," were also considered in the same sentence. Since that time many other factors have been considered. Among these are the poisons, "auto" intoxication and endocrinopathies. Some of these, or perhaps all, are known to cause nephritis sometimes, while others have not advanced out of the field of theoretic speculation.

The problem concerning the etiology of chronic nephritis has stimulated work in many directions. The greatest amount of attention, however, has been given to infection as the etiologic factor. The approach to a solution of this seems to have been by different methods, the chief of which follow:

1. From a clinical side, chronic nephritis was not infrequently seen to follow certain infections, a further discussion of which follows later. Observers, however, have emphasized the fact that frequently even in the face of very marked acute and chronic infection no nephritis follows.

2. With the discovery of the specific organisms causing the infectious diseases it was only natural that attempt be made to produce a chronic nephritis by experimental animal inoculation of these organisms. This has been done by various observers with not very conclusive results. Manneberg, Pernice and Scaglosi,<sup>2</sup> Smith,<sup>3</sup> LeCount and Jackson,<sup>4</sup> Davis,<sup>5</sup> and others have contributed much in this field; Bloomfield,<sup>6</sup> has shown that the lesions in experimental animals were likely to be spontaneous lesions rather than experimental lesions. Numerous observers have commented upon the frequency of spontaneous renal lesions in animals.

3. By urine and tissue cultures, and a comparison of these to the cultures from foci of infection, observers have tried to ascertain whether or not a relationship exists between them. Dick and Dick<sup>7</sup> found a correspondence partial or complete between the organisms found in the focus and in the urine in about 66 per cent of cases and considered this a rather significant finding. Cabot and Crabtree,<sup>8</sup> in a most exhaustive review of the literature on urinary infections,

conclude that organisms may pass from the blood stream through the kidney into urine without a renal lesion being produced.

4. A careful pathologic study of the kidneys during the various infections has also showed numerous changes which have had much weight in favor of infection. Ophuls,<sup>9</sup> using infection as a basis of glomerulonephritis, makes classification as acute, subacute and chronic.

Although infection is recognized as very important in producing acute nephritis, it is much more difficult to be certain of its importance in chronic nephritis. Other agencies than infection, such as exposure, diet, etc., without doubt must exert considerable influence, but whether they are primary etiologic factors or only secondary instrumentalities in promoting a condition already established, remains a question. It has been difficult to produce experimentally in animals lesions similar to chronic nephritis in the human by a single injection of toxin or organism. Christian and O'Hare<sup>10</sup> have by this method studied very carefully the pathology and function of diseased kidneys. Dickson<sup>11</sup> by repeated injection of small doses of uranium nitrate, and Smith, injecting organisms under Ophuls's direction, were able to produce a lesion experimentally not unlike that found in chronic nephritis of the human.

The importance of tonsillitis in the production of acute nephritis was emphasized by Hill,<sup>12</sup> who reports this to be the etiologic agent in 22 out of his series of 81 cases. This agent was considered important in 26 cases in which no definite agent could be cited.

Syphilis as an etiologic agent of nephritis has been emphasized in the past few years. Stengel and Austin<sup>13</sup> reported a series of 8 of 18 cases of nephritis which were unquestionably syphilitic. Thompson,<sup>14</sup> however, in his observations feels that syphilis has been overemphasized. In this series of 159 cases, subsequently tabulated, syphilis was found to occur in only 9 cases.

Thayer<sup>15</sup> found nephritis to occur in a certain number of cases of malaria, and quotes Kelsch and Kiener as follows: "In ordinary malarial fevers the presence of albumin is not rare in paroxysms of certain intensity but is particularly common in relapses in old sufferers in whom the kidneys are already altered. The frequent remission with relation to evidence of renal irritation is made apparent."

Though there seems to be considerable diversity of opinion on the role of infection in causing nephritis, most observers recognize its importance as influencing the process in the kidney itself or as indirectly damaging the organ through the toxins liberated.

In the present study, careful analysis of 159 cases of nephritis has been made under three classes.

1. Acute nephritis, 24.
2. Chronic parenchymatous nephritis, 25.
3. Chronic interstitial nephritis, 110.

Of the 24 cases of acute nephritis 8 attributed their trouble to an acute infection—2 to measles, 2 to diphtheria, 2 to tonsillitis and 1 each to pertussis and scarlet fever. Of the 24 cases, 22 manifested either a continuous or intermittent temperature elevation. (By fever, any temperature over  $99.5^{\circ}$  is understood.) Of the 25 cases classified as chronic parenchymatous nephritis, 16 were found to have fever. Of the 110 cases of chronic interstitial nephritis, 78 were shown to have fever and 32 none. In view of the fact that even chronic suppurative lesions frequently fail to manifest themselves by temperature elevation these figures become very striking. Febrile changes are seen to be very common in this disease, though certainly in all cases they are not definitely proved to be due to infection. It does show sufficient toxemia of some sort to cause fever.

In the 135 cases of chronic nephritis, 77 were found to have infected tonsils, 64 infected teeth, 7 syphilis, 36 some sort of chest infection, 65 colitis and constipation; 64 of these had other coexisting diseases and 52 had associated cardiac disease; 89 showed hypertension.

For lack of space complete tabulation of the cases is not given. The figures tell a story of many infections in these cases, and yet they do not tell all, for many individuals have not only one attack of a disease but many. In many the infection is a continuous process.

For emphasis attention is called to such notoriously chronic infections as tonsillitis, infection about the teeth, colitis, arthropathies, nasal and ear infection, chest infection of various types and gall-bladder disease. Endocrinopathies were noted as co-existing in 12 cases.

The question as to whether the febrile state is caused by a toxic condition due to depressed renal function or whether it is due to an infectious process, is as yet unanswered. Careful observations were made in 6 cases with febrile changes in an attempt to correlate clinical findings with the temperature curve. The renal irritation may be assumed to be manifested by urinary changes and its function was measured by the phthalein output, sodium chloride excretion, non-protein nitrogen retention (urea, creatinin) and Ambard's coefficient and McLean's index.

Only enough of the histories and findings are given to convey an idea of the case. The annexed charts show graphically what happened throughout the course.

CASE 9559.—M. L., aged forty-five years, admitted to R. W. L. Hospital May 3, 1920. Died in coma May 28, 1920.

Complaint: Weakness, rapid heart and nervousness. Her father died at sixty-nine of dropsy. Anamnesis: Varicella, mumps, measles, good recovery. Frequent colds in childhood. Pneumonia at twenty-one, following birth of child. "Rheumatism"

in arms and shoulders. At twenty-five rheumatism right hip, followed shortly by swelling of right leg, then of face and hands. Edema general and extreme. At twenty-nine, third and last child, no complications. At thirty-two a severe illness started with a papule on the right forearm; this was followed by intense swelling of right arm with dark discoloration. Period of unconsciousness followed. Recovery. At thirty-seven, attacks of vomiting associated with sharp pain in gall-bladder region. Similar attacks over seven years of time. Diseased gall-bladder removed in July, 1918, appendix and thyroid cyst also removed. Acute otitis media five

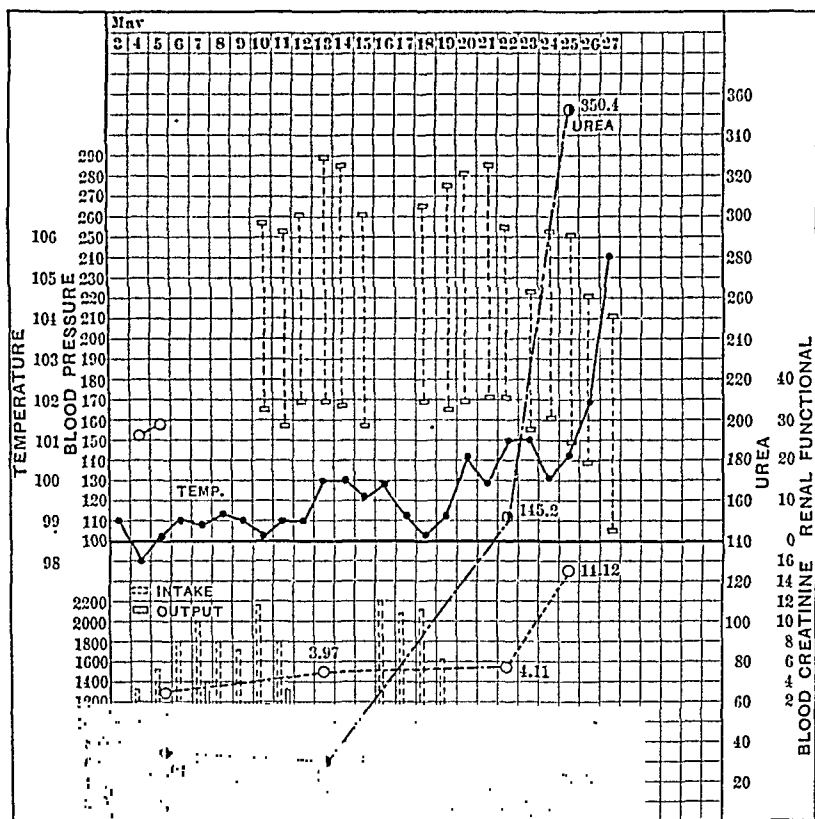


CHART I.—Case 9559.

years ago which became chronic. Pus pockets found in teeth in 1919. Chronic constipation and habitual catharsis. Onset of present illness January, 1920; weakness, roaring in head, swollen painful right leg. In March took cold; was dyspneic at night. Fatigue extreme since then.

Examination showed a patient with marked fundus changes; hypertension; blood pressure, 290–170; and with very apprehensive ideas of her future. Patient did not appear to be very sick. In a few days fever developed with renal failure, convulsions and later coma and death. Laboratory findings at first were not especially alarming, but with the rise of fever and increase in symptoms

creatinin quickly rose to 4.11 mg. and urea to 145 mg. per 100 cc blood and at death to 14 mg. and 350 mg. respectively. Urine,

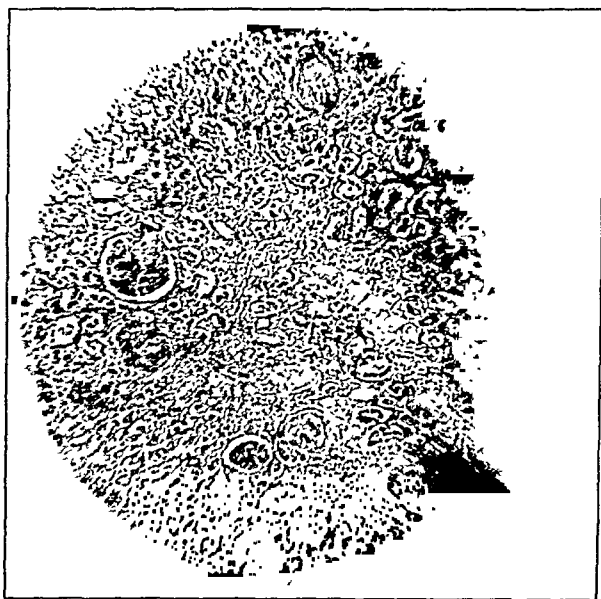


FIG. 1.—Case 9559. Section showing kidney tissue: 50 mm. x 16 mm. In this are seen areas of fibrosis in glomeruli and interstitial tissues. The same is true in regard to bloodvessels. Toward the left side one sees considerable acute parenchymatous change.

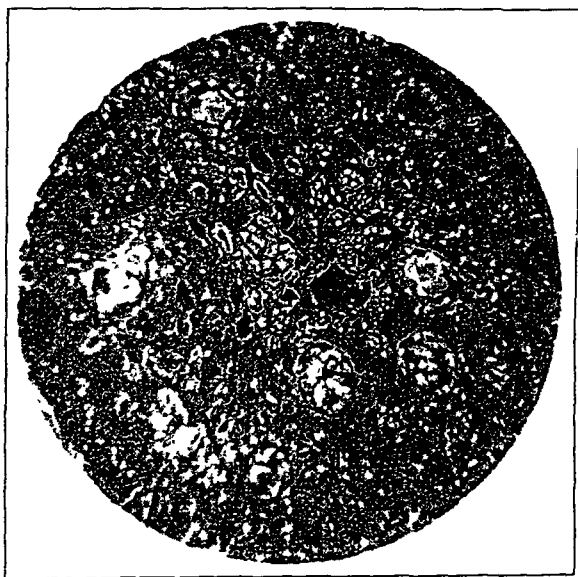


FIG. 2.—Case 9559. An area in cortex showing fibrotic change. Note almost complete absence of tubules: 50 mm. x 8 mm.

which was clear, also became loaded with red cells, granular casts and albumin—in other words definite evidence of an acute process.

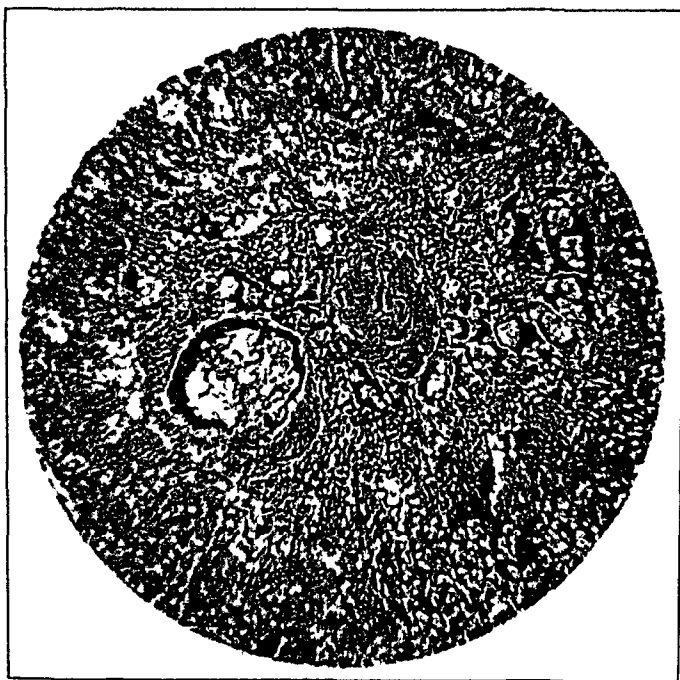


FIG. 3.—Case 9559. Area of Fig. 1 under 50 mm. x 8mm., showing one glomerulus entirely fibrosed and another very markedly so with marked fibrotic changes about the glomeruli. Note absence of normal parenchymatous kidney tissue.

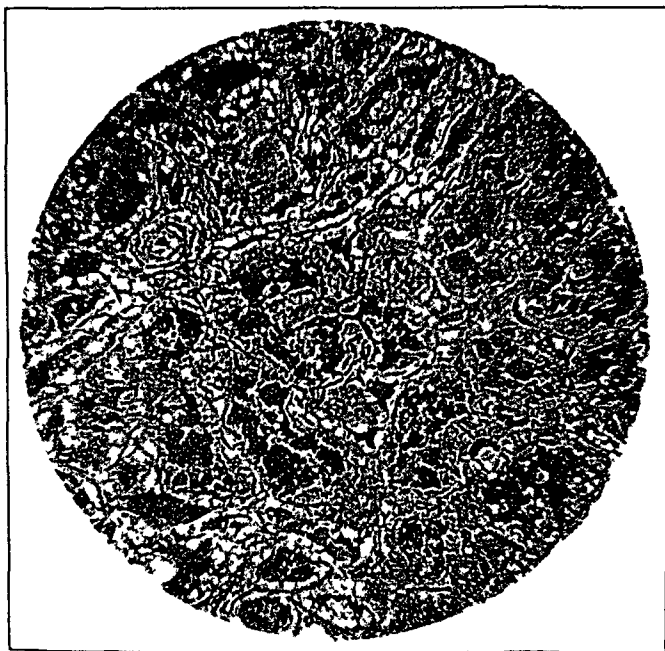


FIG. 4.—Case 9559. An area showing very marked, cloudy swelling. Necrosis and destruction of tubular epithelium. A complete absence of anything with semblance of normal kidney tissue. The epithelium of tubules is markedly swollen, necrotic, hydropic and in places completely separated from basement membrane.



At necropsy a marked acute nephritis was found superimposed on the contracted kidneys of a chronic diffuse nephritis. There was also a tendency to generalized fibrosis in other organs. Marked edema of right lung and passive congestion of left lung. Microscopic examination of the kidney corroborated the gross findings. (See photomicrographs.) No bacteria were found in the kidney substance.

To sum up, we may conclude that this case exemplifies an acute process in the kidney superimposed upon an old condition. The charts show very graphically the effect upon efficiency of kidney function by this disturbance. It is furthermore seen that this patient's life is a history of repeated infections. Some of these were latent or more or less continuous in their action. It is also seen that the trouble usually started by some infectious process. The depressed renal function seems to follow a pretty sharp parallel to the rise in temperature. Autopsy showed no terminal infection, with possible exception of the kidney.

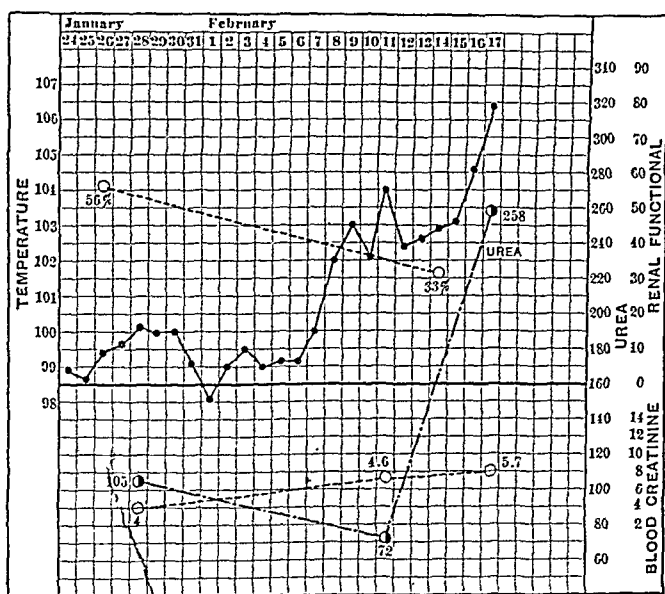


CHART II.—Case 10954.

CASE 10954.—T. J. D., admitted January 24, 1921; died February 18, 1921. Chronic nephritis with enlarged prostate. Complaint: painful and frequent micturition. Anamnesis: "Generally good health," "grippe 1912." Complicated by epididymitis. Few attacks of sore-throat throughout life. Occasional "rheumatism" in right shoulder or arm. Had two attacks of temporary paralysis.

Fell without losing consciousness, and with sharp pain in the extremities. Prostatic trouble dates back eight or ten years. In July, 1918, complete retention thirty hours. Hematuria and

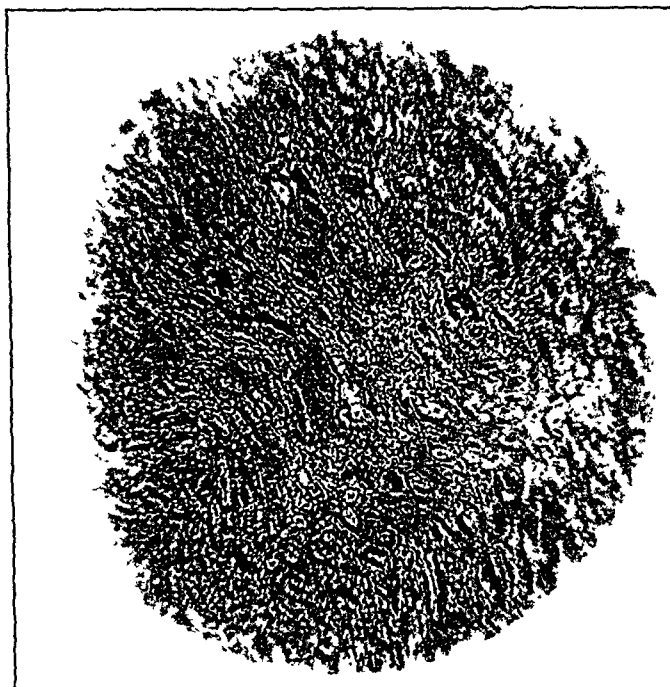


FIG. 5.—Case 10954. Showing extensive fibrosis and proliferation of interstitial tissue with area of round-celled infiltration. 50 mm. x 16 mm.

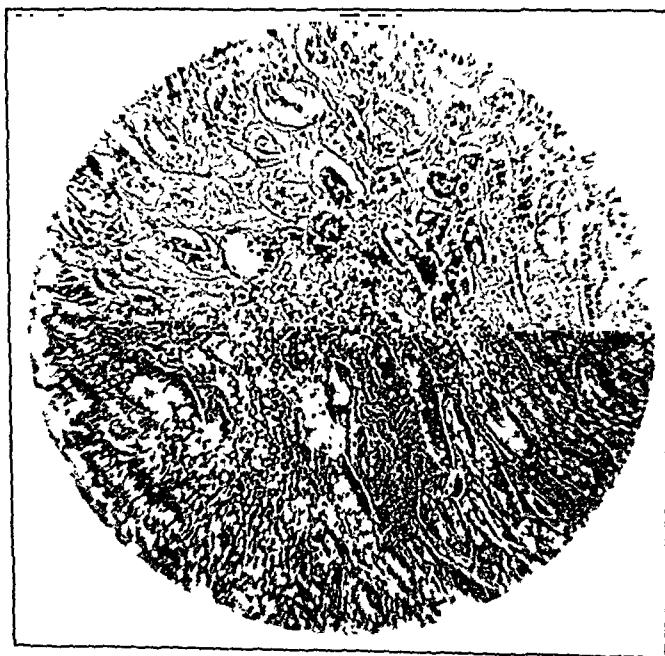


FIG. 6.—Case 10954. 50 mm. x 8 mm. showing an area of the above. Fibrotic changes and infiltration are shown more plainly.

pyuria then noted. Came to hospital January, 1921, and after trip had complete retention.



FIG. 7.—Case 10954. Showing acute changes in kidney. Note very marked coagulation necrosis and separation of epithelium from basement membrane. Round-celled infiltration is here also noted. 50 mm. x 8 mm.

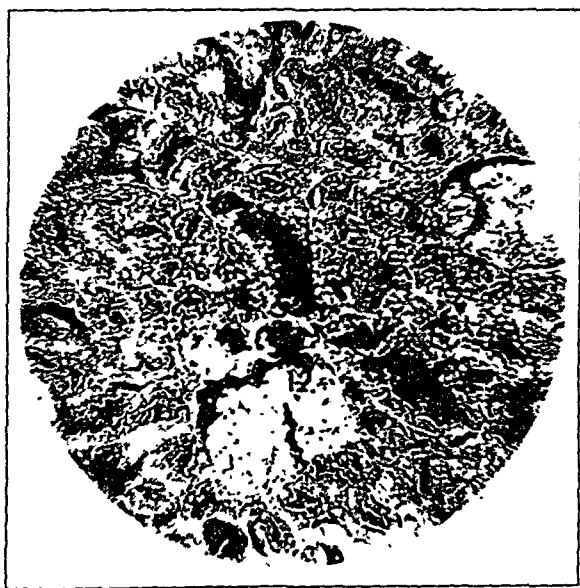


FIG. 8.—Case 10954. Section showing such marked changes as to make type of tissue almost unrecognizable. Note how markedly swollen and infiltrated the glomeruli are. 50 mm. x 8 mm.

Examination: Fairly well preserved man of seventy-two with nervous, emotional character. Chronic rhinitis, teeth foul, carious and worn. Tenderness in kidney region. Epididymis enlarged. Definite though slight edema of subcutaneous tissue of legs. In a few days became listless and some vomiting occurred. Retinal changes seen, though not marked. As fever rose there was a lowering of phthalein output from 56 per cent on admission to 33 per cent and a rise in creatinin from 4 to 4.6 mg. and later 5.7 mg. and urea from 105 to 258 mg. Three hours previous to death the blood culture was thickly studded with colonies of hemolytic streptococci (pure culture). There was almost complete urinary suppression the last few days preceding death.

Autopsy showed marked myocarditis, marked cystitis, moderate parenchymatous nephritis, purulent arthritis of left sternoclavicular costal joint. Microscopic examination of the kidney showed fibrotic areas or old lesions and areas of round-celled infiltration with acute parenchymatous changes. (See photomicrographs.)

Whatever in this case was the original process in the kidney it is certain that the final process was an infectious one. Two findings prove this: (1) A positive blood culture; (2) the known infection in the remaining part of the urinary tract. This case, clinical evidence confirmed by pathologic findings, shows very clearly the signs of depressed renal function, with rise in fever (in this case infectious).

CASE 9302.—G. B., aged forty-nine years, admitted March 2, 1920. Discharged May 1, 1920. Diagnosis: Thrombosis cerebral artery. Colitis. Nephritis, chronic interstitial. Result: Greatly improved. Complaint: Diarrhea, facial paralysis, left hemiparesis and continuous headache. Anamnesis: Usual childhood diseases. No other. Conjunctivitis five years ago. Teeth gave much trouble. Frequent tonsillitis in early life: Lymphadenitis cervicalis marked. Married at twenty; four pregnancies, three delivered prematurely. Onset one year ago; earache, facial paralysis next morning, left arm and leg weak and numb.

Examination: Somewhat anemic, undernourished female, mouth drawn to right. Teeth artificial, tonsils diseased, cervical adenitis, suppurative gland years ago.

Evidence of colitis at times very marked. Urine during febrile stage showed erythrocytes, pus and epithelial cells, a cloud of albumin, and a phthalein output of 8 per cent in two hours, which gradually increased as fever subsided to 40 per cent, with a urine showing a trace of albumin, a few hyaline casts and a few pus cells.

One of the most distressing symptoms of this patient was the colitis and the temperature seemed to fluctuate with its severity. Kidney function is also seen to be markedly depressed during the febrile change as shown by the phthalein output. Here again is a

definite acute process in the body profoundly affecting the kidney and associated with a febrile state and leukocytosis, with an accompanying troublesome colitis.

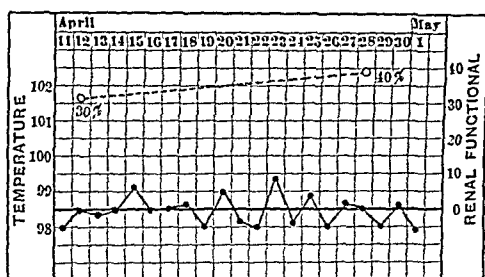
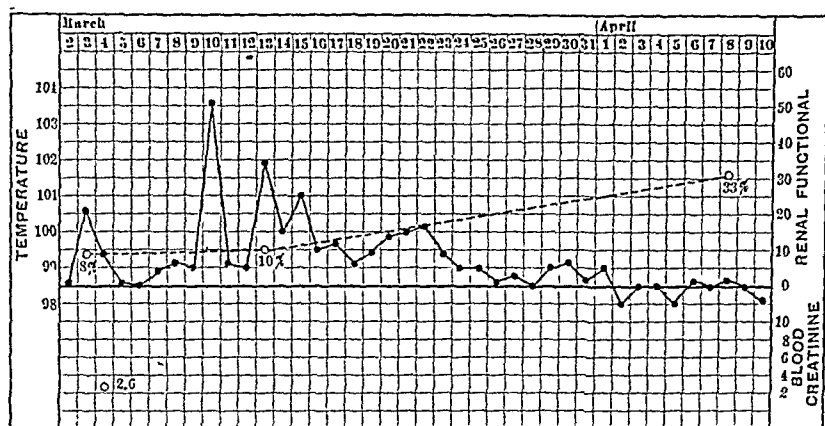


CHART III.—Case 9302.

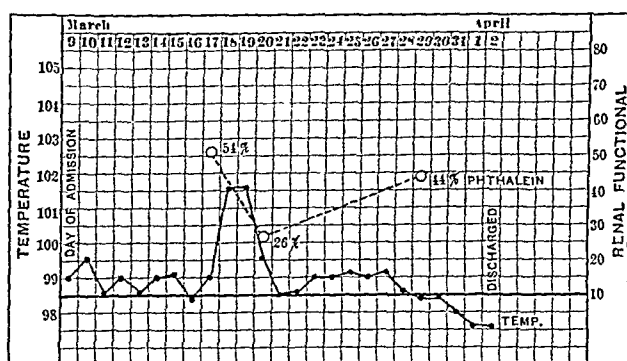


CHART IV.—Case 11185.

CASE 11185.—W. S., male, admitted March 9, 1921. Discharged April 2, 1921. This case is similar in many respects to the previous one and shows identically the same process, *i. e.*, marked depression of renal function during the febrile reaction of a mild pharyngitis.

Diagnosis: arterial sclerosis, cerebral hemorrhage (old). Anamnesis:

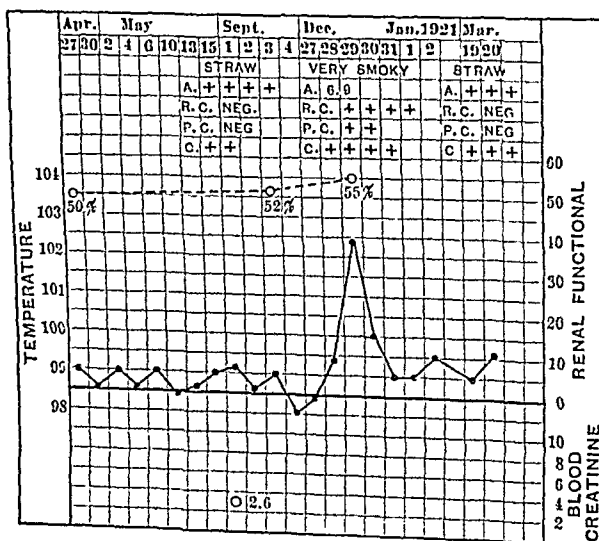
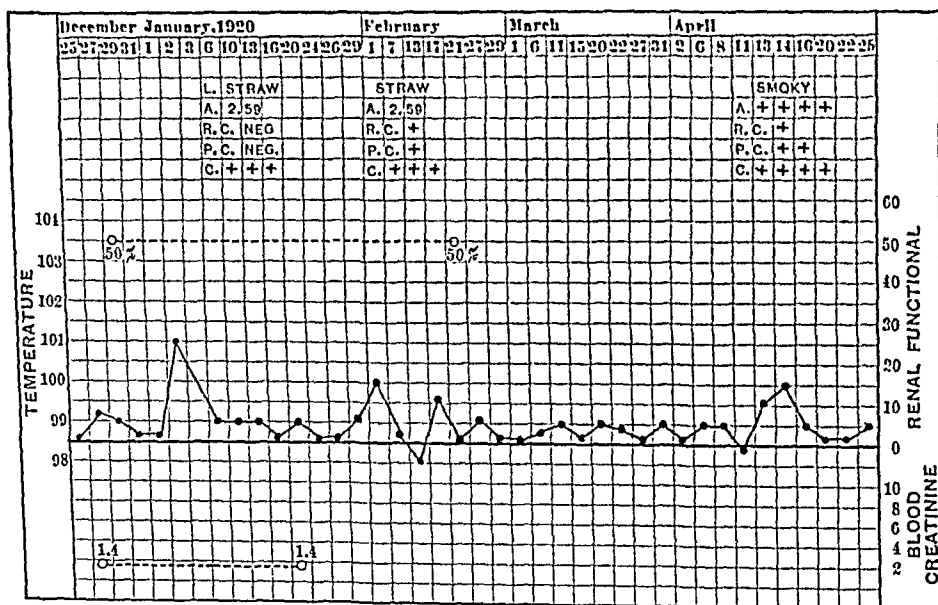
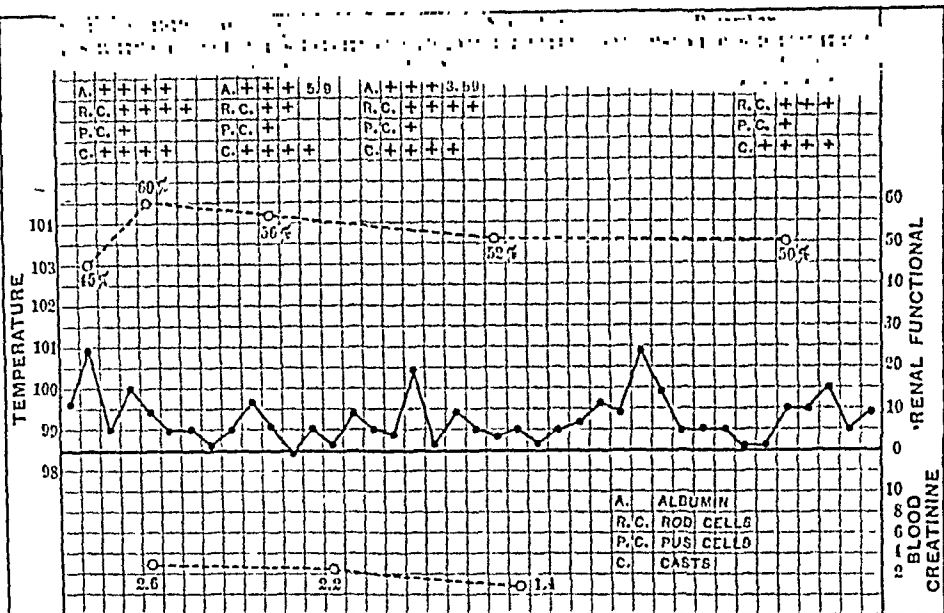


CHART V.—Case 8594.

At seventeen or eighteen had a fever; does not know its nature. Scarlatina at twenty. Occasional nycturia. Alcohol used in moderate amounts. Had "stroke" last June, condition cleared until he was almost good as normal.

Examination: Man of average build and fairly well nourished, very emotional, teeth very bad, tonsils diseased. Blood-pressure, 215; diastolic, 125. No edema. Fundus oculi changes. Note on chart the fall in phthalein excretion with rise in fever.

CASE 8594.—H. G., admitted September 7, 1919. Discharged May 16, 1920. Chronic parenchymatous nephritis. Case of nephritis due to streptococcic sore-throat of about two weeks. Negative findings until sore-throat. Arose one morning with face, feet and hands swollen, abdomen distended. (See chart for changes in urinary findings, function and fever.) Urine showed pure culture streptococcus; one year later a pure culture of tetrigenus. Blood culture normal. It is noted in this case that urinary changes with fever are quite marked, whereas function is not much influenced. This case shows a febrile condition more or less marked throughout the entire course.

CASE 9745.—I. G., aged thirty-seven years, male. Admitted June 15, 1920. Discharged September 16, 1920. Diagnosis: chronic nephritis, alveolar abscess. Anamnesis: A man with very healthy infancy and childhood. In 1917 had a trivial indisposition following overwork in a harvest field. The illness of a few days consisted of slight diarrhea and vomiting. A similar attack the following summer. Frequency of micturition for the past three or four years. Attack of severe colic six years ago. Onset six weeks ago. Family first noted puffiness of eyes and face; edema of hands and feet then followed in a few days. Hematuria on one occasion.

Examination: Generalized edema; anemia; patient alert. Mild retinal changes. Teeth in bad condition; gums swollen; tonsils buried and exude pus on pressure. (See chart and note the improvement in general function as the temperature elevation subsides. Note also how it is lowered on July 16 as the temperature rises.) This chart is inserted to show the general trend toward improvement, with a tendency for the fever to subside.

Following a tonsillectomy there was lowered phthalein excretion, an increase in edema and most marked urinary changes.

**General Discussion.** In a very complete and detailed observation of ten nephritics covering several months, Emerson<sup>16</sup> found that in many chronic cases of nephritis an acute process is in progress, variations of which were shown by increase in albumin per cent and slight rises in temperature. Though as found clinically by Emerson<sup>17</sup>

that casts are no criterion as to the amount of damage that has been done to the kidney and later emphasized by MacNider<sup>18</sup> in his

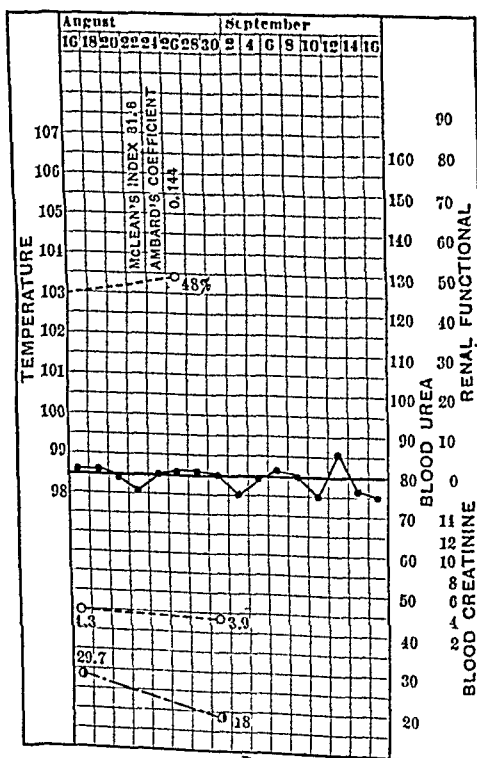
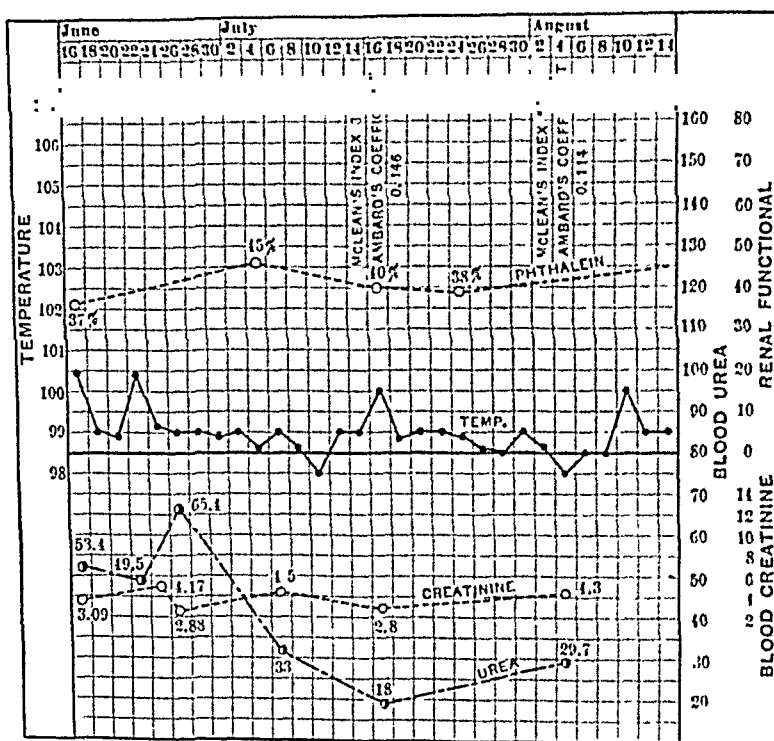


CHART VI.—Case 9745.



experimental work on dogs, yet their presence and variations can be taken as evidence of the severity of a present irritative process. These observations have been confirmed in this work. Various investigations have been conducted with attempt to measure renal function during fever or acute infectious diseases. Schlayer,<sup>19</sup> in 1912, mentioned fever as an extrarenal factor, capable of altering renal function. Lewis<sup>20</sup> quotes Ambard and Hallion (1912) as stating that urea excretion was depressed by lowering the temperature of curarized dogs. In his own observations during acute fevers, as typhoid and pneumonia, he concludes that in general there is a normal or somewhat low concentration of urea in the blood, a high rate of urea excretion, a variable concentration of urea in the urine and a high phthalein output. He furthermore concludes that *there is no constant relationship between the presence or absence of albuminuria and cylindruria and the level of Ambard's coefficient.* The latter was found to be lowered in fevers. Thayer and Snowden<sup>21</sup> noted in a few cases of pneumonia that the phthalein excretion was depressed. The pathologic picture in these cases was described as cloudy swelling, with granular degeneration of epithelium, engorgement of capillaries and the escape of a few red cells into the glomerular spaces or tubules. Five of 15 cases convalescing from acute fevers were found by Bookman<sup>22</sup> to have phthalein output below 40 per cent, the lowest being 27 per cent, and 1 to have fixed specific gravity.

In a series of acute infectious diseases, among which were pneumonia Types I and II, typhoid, articular rheumatism, and a miscellaneous group, Frothingham<sup>23</sup> in measuring function by phthalein excretion, blood-urea nitrogen and index of urea elimination concludes that these tests failed to show any consistent evidence of impaired renal function during the course and convalescence of acute infections in which ordinary urinary examinations revealed no evidence of nephritis. He found, however, a few with slightly reduced phthalein excretion. No nephritics were used. Schwartz and McGill<sup>24</sup> report some cases with acute fevers (pneumonia) as showing urea retention but draw no distinctions between nephritics and non-nephritics. Two cases convalescent from pneumonia were recorded by Longcope and Peters<sup>25</sup> as having depressed renal function (26 per cent).

It would seem from these reports that occasionally a case of acute infectious disease may show depression of renal function, though there is certainly nothing suggestive of a consistent tendency to do so. Some of the figures even suggest an increase in function. The infections studied were also self-limited, with a tendency to complete recovery.

Our work is concerned with renal function of nephritics with fever. The observations of urinary changes during these processes agree with those of Emerson.

Some of our cases, Nos. 9559 and 10954 and 9302, could be thought of as having sufficient renal tissue to carry on proper function until a superimposed acute process ensued, at which time the function was much reduced. This clinically seems to be the case. If we take fever as evidence of infection there is undoubtedly such a process present in these cases, for in all the febrile condition was at times quite marked and associated in 4 cases with definite foci of infection. Clinical findings show there was an irritative process in the kidney during the febrile period over and above that in the afebrile period, and in 2 cases this was seen to be a progressive process, parallel to progressive temperature elevation. Toward the close the urea and creatinin values mounted very rapidly. The symptoms, if possible to chart, would show a curve in every detail parallel to these curves.

Whatever the toxic condition underlying the febrile change, there is positive evidence that the kidney was very much intoxicated by it. It is thus seen that in 4 of the cases, where infection was at least one agent in action, the kidney activity was very markedly depressed. An acute element was present in the other 2 cases, the cause of which was not definite. Whether it is toxins liberated by the infection or the infection itself reaching the kidney which causes the damage is not very definitely known. Perhaps it is both. Ophuls regards the nephritis as due to an infection, there being a bacteriolysis as the organisms reach the kidney. Toxins, of which diphtheria toxin is a good example, are known to cause nephritis.

In one of the cases (No. 9745) also it is seen what a marked harmful influence tonsillectomy had, and yet the operation was done under the most ideal circumstances for that case. Other factors, as alcoholism, dietary changes, exposures, etc., have been shown to influence the course of a case of chronic nephritis in an unfavorable manner. This review suggests that infection is frequently a cause of nephritis; the cases herein detailed show that an infection may add an acute process to a chronic one already existing. Therefore infection, no matter how trivial, must be considered as a very grave menace to a chronic nephritis. This study would seem to justify the following conclusions:

**Conclusions.** 1. Many observers have noted the seeming part infection plays in the etiology of nephritis. Our observations show that during febrile elevations, either due to infection or some other agent, there is a noticeable and oftentimes measurable depression in renal function.

2. A great majority of all cases of chronic nephritis manifest temperature elevations at times throughout the course. (Acute stages.)

3. In chronic nephritis, as Emerson pointed out in his exhaustive work on *Metabolism in Nephritis*, fever with an associated increase in albuminuria shows an added acute process.

4. While function is not consistently depressed in acute infectious fever, as shown by Frothingham, Lewis and others, it is found to be so during febrile reactions in cases of chronic nephritis.

5. In chronic nephritis, as shown by fever with simultaneous untoward clinical symptoms and functional impairment as measured by phthalein excretion, urea and creatinin retention and signs of renal irritation as determined by albuminuria and sediment increase, there are superimposed acute processes.

6. The clinical findings of these 6 cases, checked in 2 cases with autopsy findings, would suggest that the course of chronic nephritis is determined by these added acute processes and that the prognosis depends in large measure upon their cessation or continuation.

NOTE.—This work was done at the Robert W. Long Hospital in the Department of Internal Medicine, at the suggestion of Dr. Charles P. Emerson, and to him the author is truly grateful for his helpful criticisms and suggestions.

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**BRACHIAL MONOPLÉGIA DUE TO THROMBOSIS OF THE  
SUBCLAVIAN VEIN.**

BY GEORGE WILSON, M.D.,  
PHILADELPHIA.

(From the Philadelphia General Hospital and the Neurological Department of the Medical School of the University of Pennsylvania.)

PHLEBITIS involving the large veins draining the upper extremity is rare. The text-books on medicine and surgery make little or no reference to involvement of the large veins of the arms, and little can be found in the literature about such a condition. As a cause of brachial monoplegia I can find no similar case on record. Marcel Gaugard, of Chateaux, France, cited two examples of subclavian thrombosis occurring in syphilitics. Haward in his monograph on phlebitis refers to Paget's report of two cases of subclavian phlebitis, one of which improved on mercury. Muscher reported a case of thrombosis of the brachial vein in a man, aged fifty-eight years, who had had syphilis. Briggs has recorded a case of thrombosis of the axillary vein in a man aged twenty-two years. In none of the above cases was mention made of a brachial paralysis secondary to the affection of the vein. Of forty-one cases of phlebitis occurring in typhoid fever only one affected the upper extremity (Osler and McCrae).

Because of the relative infrequency of brachial monoplegia due to subclavian phlebitis, and because of the rarity of subclavian phlebitis itself, I present the following cases:

CASE I.—A negro, aged twenty-five years, was admitted to the neurological service of the Hospital of the University of Pennsylvania on April 13, 1920. His chief complaint was swelling and paralysis of the right upper extremity. He had been well until the day before admission, when he took a nap on a pile of coal ashes still a little warm. He awoke three hours later because of numbness in the right arm, and he observed that the entire extremity was swollen, and that on the extensor surface of the forearm there were several blisters. There was no headache and no difficulty in talking or swallowing. There was no pain.

His family and personal history were unimportant, except that a brother died of pulmonary tuberculosis. The patient denied venereal disease.

*Physical Examination.* The eyes, ears and cranial nerves were normal, although one examiner reported a weakness of the lower half of the right side of the face, and because of this finding, in addition to the paralysis of the arm, a cerebral, cortical lesion was considered. The posterior cervical glands were slightly enlarged.

The lungs presented the signs of an acute bronchitis, and in addition those of infiltration of the right upper lobe. The heart was normal. The right upper extremity was greatly swollen from the fingers to the shoulder, and the swelling was doughy and pitted on pressure. On the extensor surface of the forearm several large blebs were seen. The radial and brachial pulses could not be felt. The tendon reflexes were absent and the extremity was completely paralyzed. Pain, touch and temperature sensations were distinctly impaired up to the shoulder. The other extremities were normal in every respect.

The sputum was repeatedly examined for tubercle bacilli and was negative. A guinea-pig injected with the centrifuged sediment of the sputum died with tuberculosis three weeks after the patient. The blood showed a mild secondary anemia with the white cells continually below 10,000. The blood culture was sterile and the Wassermann reaction was delayed negative. The urine was negative until shortly before the patient's death, when albumin and casts were present. The temperature ranged from 99° to 104°.

The patient recovered considerable power below the elbow, but practically none above that point. The edema disappeared to a large degree and the radial pulse returned as the swelling subsided. Dr. Grier Miller noted atrophy of the supra- and infraspinatus, the deltoid and the biceps muscles on May 18. The man was transferred to the medical service, where death resulted on June 6, 1920.

The diagnosis made in the case was brachial palsy due to the pressure of a thrombosed subclavian vein. The lung condition was considered to be tuberculous. The autopsy revealed miliary tuberculosis with caseation of the mediastinal, cervical and retroperitoneal lymph nodes. It was indeed unfortunate that the subclavian vein was not dissected out.

CASE II.—A negro, aged twenty-two years, single and a lead worker. The patient was admitted to the surgical wards of the Philadelphia General Hospital with a suspected lead palsy and was transferred to the service of Dr. Spiller on September 23, 1920. He gave the following history, which is supplemented through the kindness of Dr. William Bailey, resident superintendent of the receiving hospital of the city of Detroit. The patient had had three previous admissions to the Philadelphia General Hospital; the complaints, *seriatim*, were secondary syphilis, bubo and tertiary syphilis. He had worked in lead for some time but gave up that occupation because of symptoms suggestive of lead-poisoning. On July 31, 1920, he was in Detroit and went to bed feeling well. He awoke the following morning and found that he was lying on his left arm and that the entire left upper extremity was paralyzed and intensely swollen. He had no pain during the first twenty-four

hours, but suffered much after that. He went to the receiving hospital in Detroit, where about thirty incisions were made in the affected extremity, with the discharge of considerable serum and with a subsidence of the swelling. He remained in the Detroit Hospital six weeks.

*Physical Examination.* The patient was of a low mental type. The eyes, ears, cranial nerves, lungs, heart and abdomen were normal. The left upper extremity was completely paralyzed with loss of the deep reflexes and great impairment of all forms of sensation from the elbow down. The swelling had entirely subsided on admission to the Philadelphia General Hospital. The muscles of the left hand and forearm showed considerable atrophy. The blood examination revealed a mild secondary anemia with granular degeneration of the red cells. The blood Wassermann and the spinal fluid were negative.

At the time of this report a marked improvement had taken place in the patient's condition. Sensation and motion were recovering in the extremity. The treatment consisted of anti-syphilitic remedies, massage and galvanism. The early incisions in Detroit with prompt reduction in the swelling undoubtedly started the man on the road to recovery, which should be complete.

The diagnosis made in Case II was brachial palsy due to thrombosis of the subclavian vein, the etiologic factor being syphilis, whereas in the first case it was tuberculosis.

An interesting question in regard to diagnosis arose in Case I. Two excellent clinicians had, after a careful examination, considered strongly the possibility of a cortical monoplegia, with vasomotor paralysis as the cause of the edema. A slight apparent weakness of the lower half of the face on the same side strengthened this viewpoint, although the entire absence of speech disturbance and of paralysis of the tongue on the side opposite to the supposed lesion militated against the diagnosis of a cortical lesion. The confusion of such widely separated lesions as phlebitis of the subclavian vein on the right side and a cortical lesion involving the lower part of the motor area on the left side of the brain may appear to some impossible; but in a case recently under my observation, and which I will report in detail at some future date, the diagnosis of phlebitis was made by some in a case of cortical monoplegia with marked edema in the paralyzed extremity.

The question of the etiology in cases of thrombosis of the large veins draining the upper extremities naturally arises. Tuberculosis is evidently an extremely uncommon cause, whereas syphilis is probably the common cause. Dr. Turnbull, superintendent of the State Sanitarium for Tuberculosis at Cresson, has told me in a personal communication that he has no record of subclavian phlebitis occurring in the course of pulmonary tuberculosis. In

the first of my cases tuberculosis was the factor, whereas in the second case syphilis was the cause. Dr. Lockwood, of Detroit, who saw the second case soon after the onset, was also inclined to believe that syphilis was the etiologic factor in that case despite a persistently negative Wassermann. The records of the Philadelphia General Hospital show that Case II had made many visits to the venereal service of that hospital and that he had had syphilis. From a review of the cases of axillary and subclavian thrombosis reported in the literature it would certainly appear that syphilis is usually the cause of such a condition.

The production of a complete brachial paralysis in phlebitis in the cases here reported is worthy of note. The brachial plexus lies very close to the subclavian vein, being separated from it by the subclavian artery. The complete brachial palsy was due in all probability to the pressure of the thrombosed vein upon the brachial plexus.

I am indebted to Dr. William G. Spiller for the privilege of reporting these cases.

## REVIEWS.

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INDIVIDUAL GYMNASTICS: a Handbook of Corrective and Remedial Gymnastics. By LILLIAN CURTIS DREW, Director of Department of Corrective Gymnastics, Y. W. C. A., New York. Pp. 222; 100 illustrations. Philadelphia: Lea & Febiger, 1922.

THIS book deals with the normal and abnormal postures of the body, and with the gymnastic measures which may be applied for the correction of diseased conditions. It can be highly recommended.  
P. F. W.

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A TEXT-BOOK OF OBSTETRICAL NURSING. By ALICE WELD TALLANT, A.B., M.D., Professor of Obstetrics, Woman's Medical College of Pennsylvania. Pp. 276; 116 illustrations. Philadelphia: Lea & Febiger, 1922.

DR. TALLANT offers a very complete and concise text-book on this important subject. The fundamentals of obstetrics are presented in a logical arrangement, together with constant suggestions as to the practical aspect of the subject, which combine to make the book one which may be highly recommended.  
P. F. W.

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PRACTICE OF MEDICINE. A Manual for Students and Practitioners. By HUGHES DAYTON, M.D., New York. Fourth revised edition. Philadelphia and New York: Lea & Febiger, 1921.

THIS is a small "Epitome of Practice" for quick reference by "physicians" and "students." It seems to be as accurate and complete as such a volume can be. Being an epitome, it would be unfair to make any adverse criticisms, inasmuch as these would largely concern themselves with omissions and the exclusion of newer medical ideas. Of course, it is always a debatable matter as to whether or not compends justify their existence. For students they would seem to have a field of usefulness when medical courses require so much to be learned. For a physician, however, it would seem that he could refer just as quickly to a more complete and



exhaustive work and thereby obtain information of a more reliable and satisfactory character. Of this type of work it would seem that this volume is the equal of, in some respects superior to, others we have seen. In the present edition most of the revisions have been made in the section dealing with infectious diseases and functional affections of the heart.

T. G. S.

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OUTLINES FOR CASE TAKING AND ROUTINE WARD AND LABORATORY WORK AS USED IN THE MEDICAL CLINIC OF THE WASHINGTON UNIVERSITY. By GEORGE DOCK, A.M., M.D., Sc.D., Professor of Medicine, Washington University, St. Louis, Mo. Third edition revised. Ann Arbor, Michigan: George Wahr.

THIS is a very good outline guide for students beginning their practical work in medical wards. The beginner will find it an excellent skeleton to follow in history taking, in making physical examinations and in doing laboratory work on cases assigned for study.

We believe that it is a more practical thing in history taking to follow the chief complaint with the history of the present disease, instead of leaving this to the last. Patients prefer to begin with their present complaints, and then later on readily tell of their family, previous medical and social histories. The present edition has been increased in its size.

T. G. S.

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THE ETIOLOGY AND PATHOLOGY OF TYPHUS. Being the Main Report of the Typhus Research Commission of the League of Red Cross Societies to Poland. By S. BURT WOLBACH, JOHN L. TODD, and FRANCIS W. PALFREY. Pp. 222; 47 full-page illustrations. Cambridge, Mass.: Harvard University Press, 1922.

THIS report presents in full the findings of the Typhus Research Commission of the League of Red Cross Societies to Poland. The work was conducted at the St. Stanislaus Hospital, Warsaw, from March through July 1920. The report is based upon 181 cases of typhus, selected for the special wards of the commission, from the general admissions to the hospital, during this period when epidemic typhus prevailed in Warsaw. The work was directed chiefly toward determining the nature of the specific cause and the minute histopathology of typhus. Especially convincing is the experimental evidence obtained from louse-feeding experiments and by animal inoculations, in establishing the identity of the virus of typhus and *Rickettsia prowazeki*.

The extensive and painstaking histopathological study of the

lesions of typhus in man and in the experimental animals, will remain a classic, and its presentation marks the beginning of a real understanding of the pathological processes concerned in this disease. Extensive cultural and serological studies were not undertaken. Thirteen unsuccessful attempts to demonstrate the Plotz bacillus are recorded, and the diagnostic value of the Weil-Felix reaction was confirmed in 83 patients with typhus. Valuable clinical observations were made. A historical review and a summary of the present knowledge of *Rickettsia* are included. Especially valuable are the 39 full-page plates presenting 89 photomicrographs or drawings (some in color) illustrating the various developmental phases of *Rickettsia prowazeki* in the tissues, and the different stages in the development of the micropathological lesions caused by this organism.

The chapter on technic and the carefully planned controls in the experimental work would immediately win one's confidence in the reported findings, were objective demonstration and a previous knowledge of the scientific accuracy of the observers lacking. Some might contend that stains, other than the Romanowsky, would have been more valuable for histologic detail. The general plan of the work and the minute attention to details of technic may be, indeed, very profitably perused by scientific workers regardless of their fields of particular interest.

One is pleased to note that the report is dedicated to the cherished memories of seven pioneer scientists in the study of typhus—martyrs in the service of humanity—who died of this dread disease during the course of their studies.

This report and that of the American Red Cross Sanitary Commission to Serbia (Reviewed in *AM. JOUR. MED. SC.*, 1921, 162, 441), together represent a very complete presentation of the present knowledge of typhus.

J. C. S.

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AN INTRODUCTION TO THE HISTORY OF MEDICINE. With Medical Chronology, Suggestions for Study and Bibliographic Data. By FIELDING H. GARRISON, A.B., M.D., Lieutenant-colonel, Medical Corps, U.S. Army, Surgeon-General's Office, Washington, D. C. Third edition, revised and enlarged. Philadelphia and London: W. B. Saunders Company, 1921.

THIS well-known work is appearing in its third edition. It is a rather unusual event in the writing of books, for generally histories when once written remain unchanged by their authors and experience no revisions. Many phases of medical history are, however, still in the research stage and of course modern medicine is in the making. These facts have made it possible for Colonel Garrison to include

in the present edition much that has been recently learned of medieval and ancient history, as well as the developments during the recent war. New lines on the doctrine of the origin and transmission of ethnic culture has been added. New matter has been included on Chinese medicine; on the history of pediatrics; dentistry; public hygiene; military medicine and medieval lexicography; on the earlier nuclei of medical education in the United States; on recent Japanese, Spanish and Latin-American medicine, and on the work of the medical departments of armies in the European War. New biographical sketches have been added with portraits of Symphorien Champier, Villemin, Gurlt, Littre, Salkowski, Osler, Max Neuberger and others. The bibliographies at the end of the volume have been enlarged and improved; and the author's index has been made more complete and exhaustive. It is remarkable that so much has been included in a volume of such size. The whole history of medicine is briefly and clearly stated. It is intended that this book serve as a stimulus and a guide for further study in this most fascinating field. History makes all things more interesting and worthwhile. The man with historical information concerning his profession and its members must be a much better man for it. He must be a better doctor, because he has something to stimulate him, something to make his work doubly valuable. For doctors without hobbies, it would seem that medical history or some phase of it would serve quite well to supply such a need. Garrison's *History of Medicine* would seem to be a good book to begin with for a broad general idea of what medicine has been from primitive times to this day.

T. G. S.

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PSYCHOANALYSIS; ITS THEORIES AND PRACTICAL APPLICATION.

By A. A. BRILL, Ph.B., M.D. Pp. 468. Philadelphia: W. B. Saunders Company, 1922.

THIS is the third edition, the first having appeared in 1912 and the second in 1914. Reviews of the previous editions have appeared in the JOURNAL. This work was one of the first on psychoanalysis and was received by the medical public with mingled emotions. Since 1912, a period of ten years, according to the author, "psychoanalysis has made unprecedented progress both as a therapeutic agent and as an expounder and interpreter of subjects and phenomena which are not strictly medical." He further states that "as a result of war experience psychoanalysis has gained many new adherents among physicians who were hitherto unacquainted with it." In the second edition two chapters were added, consisting of the insertion of analysis of dreams, and in the present edition further clarifying cases are given, especially in regard to

some of the specific sexual phenomena, such as masturbation and homosexuality. A new chapter is added on paraphrénia. Not everyone is likely to agree with the author's conception of the successful progress of psychoanalysis; that it has grown in certain quarters, there is not any question. Almost in any city street signs are to be found which read: "Mr——" and underneath the caption, "Psychoanalyst." Readers of the JOURNAL are familiar with the number of reviews of books which have appeared on this subject. Many of these have been written by doctors of philosophy and not by medical men. In other words, the psychoanalyst has graduated from the medical into the lay field and it has become a matter of making money and charlatanism. The reviewer does not mean to imply that the medical men who practice psychoanalysis are charlatans, for without doubt psychoanalysis has many sincere students and advocates. In others, however, there is no question about this, for how can men treat the mind without knowing something of the body? In a period of ten years since the first edition of this book, psychoanalysis has not proved its case. Contrary to the view of the author, war experience has very definitely shown that psychoanalysis was unnecessary in the cure of the psychoneurotic. Psychoanalysis is on the defensive and is no longer in fashion excepting in some quarters and among certain sets of women and men who regard their journey through life incomplete without being "psyched." The present tendency is to focal infection and endocrinology. At the present time it is difficult to forecast what the next style will be. Psychoanalysis has, however, taught something. It has demonstrated a method of investigation to a great many who have not thought about it in that light, and there is no doubt that Freud has contributed a great deal to the philosophy of thought. If an experience of ten years is worth anything it has proved that a psychoneurotic patient cannot be cured purely by psychoanalysis. He can be helped but not cured. He needs something else, and that "something else" is common-sense application which only an experienced medical man has.

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MEDICAL ELECTRICITY FOR STUDENTS. By A. R. I. BROWNE, Member of the Chartered Society of Massage and Medical Gymnastics; Teacher of Medical Electricity at the Western Infirmary, Glasgow. Pp. 231; 82 illustrations. London: Henry Frowde, Hodder and Stoughton, The Lancet Building, 1 and 2 Bedford Street, Strand, W. C., 2.

THIS elementary text-book on medical electricity is somewhat of the nature of a compend and was written for students of massage and medical gymnastics. It conforms to the course of study out-

lined in the school where the author teaches and is divided into three parts, namely: (1) Electricity and Magnetism; (2) Medical Apparatus; and, (3) Electrical Treatment. In the first and second parts are discussed the principles of electricity and a brief and clear description given of the construction of apparatus used in electrotherapeutic work. The third part deals with the manner of application of the various currents, indications for their use and the effects produced. The author bears in mind the purpose of the book. He makes no attempt to delve deeply into theory, but keeps well within the scope of the understanding of the student and technician, giving them a good working knowledge that will enable them to carry out intelligently the course of treatment outlined by the physician who is a specialist in electro-therapeutics.

J. D. Z.

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EVOLUTION, GENETICS AND EUGENICS. By H. H. NEWMAN, Professor of Zoölogy in the University of Chicago. Pp. 523; 101 figures. Chicago: The University of Chicago Press, 1921.

THIS is a book on evolutionary biology, in which the subject is presented mainly by means of selections from the books and articles of the original writers. This method of compilation is very successful and serves several purposes. By it the student not only gains the information, but he feels the personalities of the various writers, and in many cases will be impelled to read further and to continue his interest along these lines. That these subjects, especially that of eugenics, are becoming more and more important at the present stage of the world's history, is being generally recognized. The book is arranged in five parts. The first is historical, giving theories of evolution from the Greeks to modern times. Evidences of organic evolution, in part two, are presented from the usual points of view, including palæontology, embryology and geographic distribution. Part three: *The causal factors of organic evolution*—is mainly taken up with the Darwinian theory of natural selections, both as Darwin presented it and as present-day scientists view it. A chapter on Professor H. F. Osborn's new tetrakinetic theory of evolution will interest modern physiologic philosophers. In the last two parts we have the results of the twentieth century attempts to formulate the problems of Genetics and Eugenics. Some of the authors quoted are: Conklin, Arthur Thompson, Guyer and Castle. Among the topics treated are: Cellular Basis of Heredity; Mendel's Laws; Are Acquired Characters Hereditary? Sex Determination; Human Conservation. The book is the result of sixteen years' experience in conducting courses in these subjects, and makes available the views of many writers within small compass.

W. H. F. A.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Musculature of Finer Divisions of Bronchial Tree and its Relations to Certain Pathological Conditions.**—MILLER (*Am. Rev. Tuberc.*, 1921, 5, 689) discusses the musculature of the finer divisions of the bronchial tree and its relation to certain pathological conditions. He studied the lungs of the guinea-pig, cat, dog and man. Because of the large amount of pigmentation present in the human lung he transferred his study to the lungs of dogs. Numerous comparative studies have shown that there is practically no difference in the arrangement of the muscles of the two lungs. The author studied the musculature of the non-cartilaginous bronchioli and their various divisions. When the subdivision of the bronchiolus is reached its character changes. Up to this point its walls have been intact, but now alveoli push their way between the muscle bands which form a sphincter about their openings into the bronchiolus and give the bronchiolus a nodular appearance. To this nodular or alveolar area is given the name *bronchiolus respiratorius*; that is, a bronchiolus which takes part in the act of respiration. That portion of the bronchial tree situated distally to the *bronchiolus respiratorius* is known as the *ductulus alveolaris* and is the last division of the bronchial tree. Each *ductulus alveolaris* and the air-spaces into which it breaks up constitute the anatomical unit of the lung. The bronchial musculature is not arranged in the form of distinct bands which encircle the bronchi and bronchioli, neither is it in the form of a continuous sheet, but it is in the form of a network. This network is made up of triangularly arranged bands, and in this way the greatest amount of strength is provided and at the same time the greatest amount

of contraction and extension of the bronchioli is permitted. At the junction of the subdivisions and the bronchiolus the bands of muscle form a sphincter about the openings; this is also true at the distal end of the *ductuli alveolares* about the openings leading into the air-spaces. In the opinion of the author these sphincters play an important role in asthma. In normal respiration the opening is of such a size that air passes in and out unimpeded. When the muscles contract, however, the size of the opening is much reduced. Owing to the larger amount of residual air which accumulates and to the greater strength of the muscles of inspiration, the normal elasticity of the lung is overcome and the air-spaces become greatly dilated. In all probability there is also a tonic contraction of the muscles in the walls of the *bronchioli respiratorii* and the *ductuli alveolares* which causes a reduction of their lumina. With the relaxation of the contracted muscle there is a general dilatation and the air again flows out freely, relieving the attack almost instantly. The author has shown quite conclusively by serial sections of the anatomical lung unit, that no muscle is present in the walls of the air cells. Confusion in other investigations has apparently resulted from faulty technic in cutting the sections of the tissue. After a careful study of the action of the muscle bands both during expiration and inspiration, Miller concludes that the action of the musculature in expiration is not passive but active and, further, that the action in regulating the tension of the air within the air-sacs deserves much more attention than physiologists have given it.

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**Pancreatic Extracts in the Treatment of Diabetes Mellitus.**—F. G. BUNTING, C. H. BEST, J. B. COLLIP, W. R. CAMPBELL and A. A. FLETCHER (*The Canadian Med. Assn. Jour.*, 1922, 12, 141). The two first-named authors attempted to demonstrate in pancreatic extracts the presence of an internal secretion acting upon carbohydrate metabolism by first eliminating the digestive enzymes in such extracts. In the first experiments, this was done by taking advantage of the fact that the acinous tissue degenerates in seven to ten weeks after ligation of the pancreatic ducts, leaving the islands of Langerhans. Extracts made with ice-cold Ringer's solution of degenerated pancreatic tissue removed ten weeks after ligation of the ducts, when injected into diabetic dogs, invariably caused a marked reduction in blood sugar and in the amount of sugar excreted in the urine. The active principle of the extract was destroyed by boiling in neutral or acid solution or by incubating for two hours at body temperature with pancreatic juice. Later, a highly potent and readily procurable preparation was obtained by extracting the pancreas of fetal calves (of less than five months' development) which did not contain proteolytic enzymes. A method was finally evolved by which an active extract, which would retain its potency for at least one month, could be obtained from normal adult ox pancreas. Daily injections of such extracts prolonged life of a completely diabetic dog to seventy days, at the end of which time the animal was chloroformed. As shown by studies of the respiratory exchange, the extract confers on the diabetic animal the power to burn carbohydrates. Collip took up the work of attempting the isolation of the active principle of the gland. As a result of this investigation an extract has been prepared from the whole gland which is sterile and

highly potent and which can be administered subcutaneously to the human subject. It is being further purified and concentrated. The effects of these preparations have been observed in seven cases of diabetes mellitus and they are similar to those observed in depancreatized animals. The fall in blood sugar occurs, and more or less coincidentally with the attainment of normal blood sugar values there is a rise in the respiratory quotient. Patients report a complete relief from the subjective symptoms of the disease. Ketonuria is abolished. In the opinion of the authors such results leave no doubt that in these extracts we have a therapeutic measure of unquestionable value in the treatment of certain phases of the disease in man. It has been found that without careful control severe toxic reactions may be encountered and this will undoubtedly be a factor in the evaluation of the ultimate therapeutic utility of the method.

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## SURGERY

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UNDER THE CHARGE OF

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**Traumatic Pancreatitis.**—DELATOUR (*Ann. Surg.*, 1921, 74, 435) says, in citing a case of subcutaneous laceration of the head of the pancreas, that the comparative absence of shock was noted, although over one-half of the pancreas was badly contused and lacerated. The principal symptoms during the first hours and during the stage of the development of the cyst were vomiting and severe upper abdominal pain occurring at intervals. In each instance these were immediately relieved by operation. Emaciation was marked until after the cyst was drained, although the boy was eating well most of the time. The ease of approach from behind and the better drainage obtained are points to be emphasized. The posterior incision is the simplest and most direct method of reaching and draining cysts or abscesses of the pancreas. If the diagnosis is not made before exploration, then as soon as the condition is clear it is better to close the anterior incision and approach the tumor through an incision parallel to the lower border of the twelfth rib on the side on which the tumor is most prominent.

**Chronic Cholecystitis Without Stones: Diagnosis and Treatment.**—MEYER (*Ann. Surg.*, 1921, 74, 439) says that aspiration of bile from living gall-bladder during operation having shown the same stigmata as that collected from the duodenum in the fasting condition before operation, definite proof has been rendered that the examination of the duodenal contents, obtained by the duodenal tube with the patient in the fasting condition deserves confidence and is to be considered



a reliable procedure. A glistening bluish soft and non-adherent gall-bladder may harbor pathological organisms in its walls, while the bile within the gall-bladder though discolored and turbid is often found sterile. This is explained by the bactericidal action of the bile as such. Cholecystectomy in cases of cholecystitis without stones, therefore, represents a prophylactic operation in many instances and is of particular benefit to those who must get well in order to earn their living. Chronic cholecystitis still belongs to the borderland cases. Although not as treacherous and deadly in its sudden attacks as the inflammation of the appendix may be, it nevertheless often undermines the patient's health. Cholecystectomy—the radical cure—should be advised after the laboratory tests prove positive. The Perthes incision is favored by the author because the abdominal wall is restored more perfectly. He also believes that it is for the best interest of the patient for the operator to advance from the gall-bladder fundus toward the common duct in the course of cholecystectomy. This will enable the surgeon to meet anatomical variations as regards the bloodvessels and cystic duct arrangement.

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**Osteochondritis of the Upper Extremity.**—CALVE (*Jour. Ortho. Surg.*, 1921, 19, 489) says that this affection is not clearly individualized except in radiographic findings—the characteristic lesion shows the femoral head in place, the clear articular space enlarged, the epiphyseal nucleus modified both in form and substance, being flattened and fragmented. The term osteochondritis appears defective for it seems to indicate an affection in full inflammatory evolution. The author prefers to substitute the term “coxa plana” proposed by Waldenstorm. The characteristic of the disease is an acquired articular malformation with flattening of the superior femoral epiphysis and the regeneration of the epiphyseal osseous nucleus. The articular contacts take place in defective fashion and frequently bring about, under the influence of fatigue, painful phenomena comparable to those of all articular malformations.

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**Fractures of the Femur. End-results.**—HENDERSON (*Jour. Ortho. Surg.*, 1921, 19, 523) says that the younger the patient the easier the application and carrying out of conservative measures, although occasionally even with babies difficulty will be encountered in satisfactorily engaging the ends of bone. When this occurs open operation should be resorted to. In vigorous adults under proper surroundings the open operation, using beef-bone plates or, if necessary, metal plates as internal fixation, has been more satisfactory than conservative measures in the author's experience. In a well-equipped fracture ward in a hospital with trained attendants, conservative measures would give equally good functional results. The author states that he will operate more in the future on patients in good general health. This does not apply to patients with fractures of the neck of the femur for which the Whitman abduction method gives perfect control of the fragments. Statistical reports of follow-up work in the Mayo Clinic are recited.

**Report of Commission on Stabilizing Operations upon the Foot.**—Cook and STERN (*Jour. Ortho. Surg.*, 1921, 19, 437) say that metal plates, wires, screws, nails and bone grafts are objectionable and unreliable. Arthrodesis gives excellent results in lateral instability, especially where there are good calf muscles. The best results are to be found after the triple arthrodesis of Ryerson or the subastragalar arthrodesis of Davis. Astragalectomy with backward displacement of the foot when done after the method of Royal Whitman—(1) for calcaneus and calcaneo-valgus, (2) for dangle feet, and (3) for lateral deformity—gives by far the best results. In some cases the result has been so perfect and the foot so symmetrical that it would have been difficult to tell that the foot had been operated on, had one not been able to see the scar. Horizontal transverse tarsectomy after the method of Davis gives, as a whole, inferior results to the astragalectomy and is a more difficult, bloody and less surgical procedure. Living ligaments, after the methods of Gallie, Putti, Peckham and others, have given isolated successes but as a general rule have not been successful and are not held in universal esteem. A great many of the fixation cases that were examined were done after the ordinary tendon transplantations had failed and it would seem that the place for tendon transplantation is as an adjuvant to a “stabilizing operation.”

## THERAPEUTICS

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**Treatment and Prevention of Pellagra by a Daily Supplemental Meal.**—G. A. WHEELER (*Jour. Am. Med. Assn.*, 1922, 78, 955) reports the results of treating 54 definite cases of pellagra at an out-patient clinic of the U. S. Pellagra Hospital at Spartanburg, S. C. The treatment consisted solely of one daily supplemental midday meal of fresh meat or fish, vegetables, fruit, bread and butter and either sweet milk or buttermilk. The patients were, for the most part, cotton-mill operatives residing near the hospital. All were ambulant cases of a moderate degree of severity. With the exception of the supplemental meal, there were no significant changes in the domestic environment or personal habits. The eruption and, with one exception, the subjective symptoms disappeared within a few weeks of beginning the treatment and there was no evidence of a recurrence while in attendance at the clinic. Of a total of 48 anniversaries passed by this group of patients from the time of their first attacks to the date of admission to treatment, there had been 44, or 91.6 per cent, regular, consecutive,

annual recurrences, while of a total of 25 anniversaries passed under treatment there was not a single recurrence. Within from five to eight months after discharge from treatment, 7 patients developed recurrent attacks, 5 of whom had had annual recurrences prior to treatment and had passed one or more anniversaries under treatment without return of symptoms. A deprivation period of less than five months is indicated. One supplemental meal of fresh meat or fish, milk, vegetables, fruit, bread (either wheat or corn) and butter was adequate to relieve the symptoms and to prevent recurrences in patients continuing in the environment in which the disease had originally developed or had previously recurred.

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**Hypopituitarism and its Treatment.**—LISSER (*Endocrin.*, 1922, 6, 15) writes that the clinical manifestations of hypopituitarism in a given case depend on the exact amount of normal secretion lacking or in excess, the time in the life cycle of the patient when this excess or lack originated, and the sex of the individual. A normal-sized sella turcica does not rule out pituitary disease. The signs and symptoms of hypopituitarism usually group themselves into three fairly well defined syndromes: (1) The Levi-Lorain type of pituitary infantilism, with skeletal undergrowth and genital aplasia, but without adiposity; (2) the Fröhlich type of dystrophia adiposogenitalis, with skeletal undergrowth and genital aplasia and adiposity; (3) the less frequently recognized Neurath-Cushing variety, showing skeletal overgrowth with genital aplasia and adiposity. The author gives case reports of the above three types. Other members of the family frequently show similar ductless gland disturbances, and in such cases there is probably some defect in the development of the gland. In some instances hypopituitarism appears to have followed an acute infectious disease, or tumors or injuries may appear to be responsible. The prognosis depends upon the nature of the lesion. In general, early diagnosis and long-continued treatment give the best hopes for recovery. Sometimes pituitary therapy gives gratifying results; but it often is extremely uncertain. We have no adequate ideas as to dosage.

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**The Present Status of the Doctrine of Colds.**—BICKEL, (*Deutsch. med. Wchnschr.*, 1921, 47, 780). The blood is altered by cooling locally. The effect is distal from the affected area and is dependent upon the duration and intensity of the cold; it is more marked if the individual is overheated. The effect on the blood is a paralysis of its phagocytic properties, stoppage of formation of bacterial antibodies; and probably substances are formed which have a harmful effect on the capillary wall. The damaging of the protective mechanism permits the bacteria present in the respiratory tract to thrive. Bacterial infection is therefore the secondary result of the distally damaged blood brought centrally. The infection itself is the result of the "cold" but not the cause.

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**A Spontaneous Attack of Tetany During a Paroxysm of Hyperpnea in a Psychoneurotic Patient Convalescent from Epidemic Encephalitis.**—BARKER and SPRUNT (*Endocrin.*, 1922, 6, 1) describe a patient, who was a psychoneurotic boy of eighteen, convalescent from encephalitis,

had attacks resembling petit mal, functional hyperpnea and a single spontaneous attack of tetany. Right-sided abdominal adhesions were found with cecal stasis, constipation and gastric hyperacidity. There were also present signs of mild endocrinopathy. The single attack of tetany occurred during the first examination and is interpreted as due to disturbed acid-base equilibrium secondary to the prolonged hyperpnea. When the patient was left with one companion in the room and his excitement quieted down, the deep breathing stopped and the tetany disappeared. No chemical study of the blood was made. The petit mal attacks may be due to anatomical changes following the encephalitis. Complete freedom from symptoms was obtained by rest and upbuilding treatment, with isolation from home and family, occupational therapy and psychotherapy; appropriate treatment was directed against the constipation and gastric hyperacidity. The case is reported in detail and the origin of tetany is discussed.

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**The Effect of Yeast Extract upon the Secretion of Gastric Juice in Human Beings (Cenovis stomach tablets).**—KLEIBATT (*Deutsch. med. Woch.*, 1921, No. 21, 47, 1024). Yeast extract has the same chemical composition as meat extract with the exception of creatin and creatinine. Immediately after ingestion the acidity of the stomach is increased. Normally acidity reaches its height in a half hour and then gradually declines. With the extract there is an increased free and total acidity, the peak of the acidity curve is reached sooner and sustained longer, while secretion itself is prolonged.

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**The Question as to the Sensitiveness of the Human Organism to Adrenalin.**—CSÉAI (*Deutsch. med. Woch.*, 1921, 33, 953) found that if adrenalin in doses of 0.5 to 1.0 mg. had no effect when injected subcutaneously, intramuscular injections of the same amounts had also no effect or very little. If, however, the adrenalin was given intravenously in doses of 0.02 to 0.03 mg., a rise in blood-pressure always occurred. In no case did he fail to get a rise in blood-pressure from the intravenous administration, regardless of whether or not reactions were obtained by the other methods of administration.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**Congenital Syphilis in Institutional Children.**—LAWRENCE (*Jour. Am. Med. Assn.*, 1922, 78, 566) made a study of the blood in children in institutions. A total of 11,205 persons were examined, ranging from two to twenty-one years of age, with an average of ten years. It was found that 68 per cent of the specimens gave a negative reaction when tested

with two antigens and that 122 specimens, or 1.1 per cent of all, gave a four-plus reaction to both antigens. This small number of positives was rather a surprise, for, even if the one-plus specimens were added to the four-plus, there would be only 2.3 per cent of positive reactions among this large number of children. The physical findings were also somewhat surprising: some children who were found positive by blood examination had always seemed perfectly well and healthy, while some others who had histories of symptoms more or less suggestive of congenital syphilis, gave negative reactions. More than 700 white children were given a superficial physical examination. One case of alopecia was found in the group having positive reactions. Rhagades were observed in 10 per cent of the positives, 0.3 per cent of the doubtful and not at all in the negative cases. Teeth of the Hutchinson type were observed among the positives and doubtfuls, but not among the negatives. Families of 14 children with positive Wassermann reactions, of 263 children with doubtful reactions and of 66 children with negative reactions were investigated. It was found that in the group of those having positive reactions, 82 per cent of the relatives tested were positive. The findings in the doubtful group showed that of 173 relatives tested, 23 or 13 per cent had definite four-plus reactions, while the reactions of the children themselves could only be classified as doubtful.

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**The Antiscorbutic Value of Dried Fruits.**—ECKMAN (*Jour. Am. Med. Assn.*, 1922, 78, 635) made feeding observations on four series of guinea-pigs, weighing from 150 to 200 gm. each at the start. The basis of their diet consisted of a half-and-half mixture by weight of alfalfa meal and wheat flour, to which 1 per cent of sodium chloride was added. The dried fruits used were peaches, apricots, apples, pears, prunes, cherries and loganberries. Precautions were used to insure a uniform quality of these products. Water and the moistened alfalfa-flour mixture were fed freely, and varying amounts of the fruits were used. The animals were weighed every day or every other day, as their condition seemed to demand. When scurvy symptoms were prominent and marked loss of weight occurred, the amount of fruit was increased in the effort to prevent a fatal ending of the disease. In the first two series, which were preliminary in character, 0.5 and from 1 to 2 gm. respectively were used. All of these animals died with scurvy symptoms or secondary infection within from two to four weeks, although those receiving peaches, apricots and apples showed greater resistance to scurvy and to infection. In the third series, in which eight animals were observed, two received apples and the others received either peaches, apricots, pears, prunes, cherries or loganberries. The results were convincing only in the case of peaches and seemed promising in the cases of apricots and apples, although less so in the former. The fourth series was run to determine whether or not an animal could be kept alive for any length of time on less than 4 gm. of peaches a day, and to check up the previous series in regards to apples and apricots. He found that 3 gm. of peaches sufficed to prevent scurvy symptoms only for a period of thirty-five days, and on the appearance of these signs an increase to 4 and even to 5 gm. did not effect a cure. The apricots failed entirely to substantiate the former observations. Two animals fed on 3 and 4 gm.

of apples also showed scurvy symptoms promptly, although the one receiving 4 gm. lived for forty-five days after the apple ration had been increased to all that it would take. These observations would indicate that only one of the dried fruits tested contained sufficient antiscorbutic vitamin to maintain the life of a guinea-pig, and this one was dried peaches.

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**Craniotabes in Infants.**—MARFAN (*Paris Méd*, 1921, 11, 493) claims that true craniotabes is of rachitic origin as a rule, but it is the manifestation of a very early rickets, which begins during intrauterine life or before the age of three months. He believes that at all ages the principal cause of rickets is syphilis. Rickets from this cause is distinguished by its early onset, by the tendency of lesions of the bones of the skull to develop, and by the accompanying anemia and frequent chronic enlargement of the spleen. Rickets with much deformity of the bones is nearly always of syphilitic origin. When caused by any other factor the rickets usually spares the skull and the involvement of the epiphyses and ribs are more prominent. In cases of craniotabes it is important frequently to change the position of the infant's head, not allowing it to lie on the back or one side of the head too long, as there will develop a tendency for the head to become deformed in shape. The discovery of craniotabes demands the necessity of searching for the cause and of giving specific treatment. Marfan feels that in the present-day knowledge it is improper to consider this as merely delayed ossification.

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**Effectiveness of Infant Welfare Clinics from a Medical Point of View.**—KNOX and POWERS (*Jour. Am. Med. Assn.*, 1922, 78, 707) found that standardized medical supervision of children under three years of age, in conjunction with careful home visiting and instruction by nurses, was highly effective in reducing mortality. In 1920, 13,036 children under three years of age were enrolled in The Babies' Milk Fund Association of Baltimore. Those who were brought into the clinic at least three times were classed as Group 1. Of these, there were 4366 children, both white and colored; those who were brought less than three times or not at all were called Group 2, of which there were 8670 children, both white and colored. The general mortality for both white and colored children in Group 1 was 18 per 1000, as compared to 47 per 1000 in Group 2. The greatest relative reduction in the number of deaths occurred in the negro children, who showed a mortality in Group 1 of 19 per 1000 in Group 2 of 72 per 1000. The reduction in the death rate was most striking in malnutrition, summer complaint and dysentery. The deaths of white and colored together from these diseases were 2 per 1000 in Group 1 and 21 per 1000 in Group 2. In Group 2 the negro children showed a mortality 40 times that in Group 1, in which it was 6 per 1000. Deaths from respiratory causes in children under three years of age may be slightly reduced by the promotion of good nutritional development. In negro children the prevention of rickets by the use of cod-liver oil reduces the incidence of respiratory disease. From respiratory infections the mortality of white and negro children combined was 11 per 1000 in Group 1 and 16 per 1000 in Group 2. It was 8 per 1000 in white children in Group 1 and 10 per 1000 in Group 2, while among the negro children it was 15 per 1000 in Group 1 and 31 per 1000 in Group 2. Diphtheria and syphilis offer the greatest

opportunities of applying preventive and curative measures of the remaining diseases which may occur in childhood. The mortality of white and colored children combined from miscellaneous diseases was 5 per 1000 in Group 1 and 8 per 1000 in Group 2. In Group 1 among the colored children the mortality was 3 per 1000, while in Group 2 it was 17 per 1000. The most valuable contribution toward the prevention of disease and death among children to be made by the nurse, is the teaching of the mother to keep her children under competent medical inspection.

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**Results Following the Administration of Alkali Phosphates to Spasmophilic, Rachitic and Normal Children.**—CALVIN and BOROVSKY (*Am. Jour. Dis. Children*, 1922, 23, 238) report a number of cases upon whom these observations were made. They found that the administration of from 0.55 to 0.60 gm. of potassium diorthophosphate or sodium diorthophosphate per kilo of body weight per twenty-four hours to the infants neither activated latent spasmophilia nor produced symptoms resembling spasmophilia. In one case of rickets the electrical excitability approached the spasmophilic reaction for about thirty-six hours, although no other manifestations of tetany were present, notwithstanding the fact that the potassium phosphate was continued. Several of the cases selected were at the most susceptible age for spasmophilia to develop. Several of the babies showed marked evidence of rickets, supposedly making them more prone to develop spasmophilia. Even the superimposing of acute intercurrent infection in a number of cases, plus the administration of the phosphates did not precipitate spasmophilia or spasmophilic manifestations. Three of the patients just recovered from active spasmophilia were observed and yet it could not be precipitated by administering the phosphates. These patients had recovered from active spasmophilia on receiving phosphorized cod-liver oil, which is known to increase the phosphorus content of the blood. All in all, the authors were unable to confirm the results of Jeppson and Klercker.

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**Studies on Experimental Measles.**—DUVAL and D'AUNOY (*Jour. Exper. Med.*, 1922, 35, 257) observed that guinea-pigs react specifically to intracardiac injections of defibrinated blood from cases of human measles. There was a definite and constant rise in the temperature, and a coincident decrease in the total number of leukocytes after an incubation period of from nine to twelve days. The guinea-pig reaction is produced with human blood only during a certain phase of the disease, which corresponds approximately to the eruptive stage. Thirty-six hours prior to the eruption and twenty-four hours after the temperature is normal the human blood gives rise to no reaction in this animal. The reaction follows with greater frequency in animals inoculated with measles blood obtained at the height of the eruption. Guinea-pigs which react and recover are not susceptible to reinoculation with measles blood if tested over periods of two weeks to three months after recovery. Guinea-pigs receiving normal human blood injected intracardially do not react with leukocytic or temperature changes. The authors conclude that propagation of the virus is obtained by passage of the blood from infected guinea-pig to normal guinea-pig, and that such passage seems to increase the virulence.

## OBSTETRICS

UNDER THE CHARGE OF

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**The Part Played by Lutein Cells in the Ovary in Causing Uterine Hemorrhage.**—ROUVILLE and SAPPEY (*Gynécologie et Obstétrique*, 1922, No. 1, 5, 1) contribute a paper upon this subject in which they review the literature and quote reported cases, adding their own with illustrations. Their studies have been made on patients who suffered from uterine hemorrhage and in whom it was necessary to perform abdominal section, dealing with diseased tubes or the uterus, as might be necessary. The ovaries removed were subjected to microscopic study and a summary of the conditions found in each case is added to the history of the case. Their results are of interest to the obstetrician because at the present time it is believed by some that the corpus luteum may be of value in some of the disorders of pregnancy, notably in the toxemia of early gestation. It is interesting to note that in these cases there was one condition which seemed to be present in practically all; that was, an ovarian degeneration accompanied by the disappearance or great diminution in number of luteum cells. From their observations the writers believe that menstruation is caused by an internal ovarian secretion, produced by luteum cells which are practically identical with the interstitial cells of the internal theca of the ovarian follicle or the cells produced by the corpus luteum itself. Where the function in these cells is in excess, a pathological hemorrhage is produced which may be irregular, but is usually less in quantity than the average normal menstruation. Hypofunction may lead to amenorrhea. In various conditions which are practically part of these, it seems to be a question of degree rather than the development of any other condition. In estimating the secretory value of an ovary, the macroscopic appearance and the presence or absence of cysts is of no practical value. A histological examination alone can determine the state of the ovary.

In connection with the previous article is a paper in the same journal by LÉVY-SOLAL, LELIÈVRE and VIGNES. They describe the case of a primipara aged thirty, who came to the Baudelocque Clinic at the advice of a midwife who had been attending her in her pregnancy. The previous history was unimportant, but the size of the abdomen was abnormal, which attracted the attention of the patient and the midwife. On examination the abdomen seemed very prominent. There was swelling of the tissues about the pubes, and also the lower extremities. The fundus of the uterus was 42 cm. above the pubes; the circumference of the abdomen above the umbilicus, 119 cm.; on palpation the head of the fetus was made out in the right hypochondrium, and on further palpation it was found that the neck of the child had been drawn upward some distance above the pubis. There seemed to be a mass which filled the posterior cul-de-sac and which seemed prolonged toward the patient's left side. A diagnosis of pregnancy at



the ninth month complicated by the presence and impaction of a cyst of the left ovary was made. The patient was put to bed and labor was expected about the twentieth of September. On the twenty-second the membranes ruptured prematurely and a greenish liquid was expelled; the uterine contractions were infrequent. After some time in labor the patient was operated upon by abdominal section and fluid found in the abdominal cavity. A large multilocular cyst of the left ovary was present on the left side of the pelvis and adherent to the bowel and surrounding tissue. There was also a cyst in the right ovary of much similar size. The uterus was first emptied by Cesarean section and the cysts then removed. Hemorrhage was prevented with some difficulty through the size and position of the utero-ovarian arteries. The patient made a good recovery without complications and left the hospital in good condition with her child doing well. The child died some months afterward from measles. The mother's condition a year after the operation was very good. The writers conclude from their study of the subject that it is both possible and probable for such tumors to take their origin from detached appendices-epiploica, and this theory accounts for a large number of these cases. These unusual bodies coincide practically with ovarian multilocular cysts and develop with especial rapidity during pregnancy. They are accompanied by ascites. They are composed of a central fatty zone and a cortex formed of cells and of fibers interwoven. In addition there exists an endothelial internal lining, which is different from that described in any previously published report. The peripheral portion of these tumors is not stratified and but little developed in layers. It is composed of fibers. It is especially striking to observe that cells exist throughout the entire extent of these fibers. There are certain bodies in these cells which contain the bloodvessels, and which were found in a condition of degeneration. There exists a center of calcareous degeneration, and various types of cells were present, leading to the belief that this was a form of evolution which had terminated in degeneration. The pregnancy had evidently been a stimulus to the formation of luteum cells of unusual size and in great abundance.

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**An Unusual Case of Ectopic Pregnancy.**—ROSENDOHN (*Jour. Am. Med. Assn.*, March 11, 1922, p. 729) reports an unusual case of ectopic pregnancy from the New York Lying-in Hospital. The patient, aged thirty-seven, was admitted with ruptured ectopic gestation for which the right tube and ovary were removed. There was considerable hemorrhage and a citrate transfusion of 900 cc was performed. On the second day the patient developed consolidation on the right lower lobe; two days later a right parotitis, which increased as the pneumonia began to clear up. In about ten days the parotitis had disappeared.

On obtaining a complete history it was found that four years previously the left tube and ovary had been removed for a ruptured ectopic gestation, there being considerable hemorrhage at this time. Two days after this operation the patient had pneumonia, and seven days afterward a marked left parotitis. This was incised, and a culture made from the serum showed *Staphylococcus aureus*. The patient made a good recovery. One and one-half years after this first ectopic gestation the patient was admitted in active labor without engagement and was

delivered by an abdominal section from which she made an uncomplicated recovery.

The patient's unusual experience consisted of left ruptured ectopic pregnancy with pneumonia and left parotitis; abdominal Cesarean section and right ruptured ectopic pregnancy with pneumonia and right parotitis

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**An Unusual Recovery from Puerperal Septicemia.**—ROBINSON (*Lancet*, February 25, 1922, p. 371) reports, with a temperature chart, the case of a primipara, delivered by forceps, who two days afterward had chill and temperature 104.2° F. The uterus was irrigated with a chlorinated solution and a stock vaccine of 10,000,000 streptococci was given. The culture taken from the uterus showed streptococci. Antistreptococcus serum was given for thirty hours, in all, 120 cc. A dental syringe was used and the serum was injected into the muscle substance, and about 135 punctures of the skin were made to obtain a very large area for simultaneous absorption. On the ninth day 2 drams of fluid extract of ergot were given to lessen the risk of air-embolism. The midwife who attended the patient in her home had a felon on her finger, and the case previously attended by her was septic and also gave streptococci in the uterine secretion. Her two cases before had mild fever. It was thought that the organism quickly increased in virulence by passing through a short sequence of cases.

The patient seemed to be almost moribund before the antistreptococcic serum was given. She rallied speedily and recovered. Four hours elapsed between the dose of 30 cc and 60 cc antistreptococcic serum.

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**Intracranial Bleeding in the Newborn.**—HENKEL (*Zentralblatt für Gynäkologie*, 1922, No. 4, p. 129) calls attention to the importance of asphyxia as a cause for intracranial bleeding in the newborn. He describes in detail 12 cases. In 3 of these the child was delivered by forceps; 1 was a case of rupture of the mother's uterus, and there were 2 cases where evidently excessive pressure trauma had to do with the intracranial bleeding in the fetus. This leaves 6 or one-half of the cases where asphyxia was the only possible cause which could be detected. In these cases autopsy showed minute hemorrhage in the muscle of the heart or endocardium; a general condition of cyanosis which was lacking in cases with bleeding following traumatism. Where there has been injury to the cranium by pressure and a cerebral vessel is ruptured, the bleeding is often so profuse that the bloodvessels in other portions of the brain and cranium are empty, and this hides the general condition of the circulation. If it is true that the bleeding is the result of asphyxia, this has an important bearing upon the question of treatment. The heart sounds of the child should be watched during labor, and a change in rhythm from very rapid to very slow should be promptly noted. For practical purposes the heart sound of the child furnishes the only indication we have as to the danger of asphyxia before its birth, and this at present is our only definite indication concerning its vitality. The question also arises whether we should not deliver more promptly with the forceps whenever it is possible, if the heart sounds of the child show variation. If the forceps delivery

would be difficult and the head be subjected to considerable pressure, evidently this would add greatly to the dangers of a child already partly asphyxiated. So far as the relief of asphyxia is concerned, the use of forceps should be limited to cases in which the head is on the pelvic floor and in which delivery can be very readily and quickly accomplished. In cases where there is considerable resistance in the pelvic floor and perineum and the child is threatened with asphyxia, a central incision and prompt delivery may bring about a favorable result for both mother and child.

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## **PATHOLOGY AND BACTERIOLOGY**

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UNDER THE CHARGE OF

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**The Concentrating Activity of the Gall-bladder.**—Having determined that the simultaneous flow of bile from different regions of the dog's liver has nearly the same amount of pigment per cc, ROUS and McMASTER (*Jour. Exper. Med.*, 1921, 34, 47) studied the ability of the gall-bladder to concentrate bile, employing as a criterion the pigment strength of a sample collected throughout the period of experiment from a duct branch. After control observations and various series of experimentations, it was found that "the extent and rapidity of the concentration are alike remarkable," the empty gall-bladder left to fill from the liver, reducing its bulk 10.8 times in twenty-two and one-half hours. Another gall-bladder, left distended with a bile of known constitution and receiving in addition fresh bile from the liver, concentrated the secretion 8.9 times in twenty-two hours. "A series of five emptied bladders concentrated the bile coming to them in about twenty-four hours on the average of 7.1 times, or a little more than the 6.4 times of seven organs-left full. As shown in a companion paper, the bile ducts do not withdraw fluid from the secretion they carry but tend to dilute it. In discussing the various functions of the normal gall-bladder, the writers remark that "the fact that few ills follow upon removal of the normal gall-bladder means merely that the body has adapted itself to the loss, not that the loss is unimportant," and "in this connection the surgeon would do well to remember that uncertainty as to function and confidence in readjustment are at best questionable motives for adventures in ablation."

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**Physiological Causes for the Varied Character of Stasis Bile.**—In a sister publication, ROUS and McMASTER (*Jour. Exper. Med.*, 1921, 34, 75) conducted several series of experiments on dogs, cats

and rhesus monkeys by tying and cutting the bile ducts to investigate the reasons for the varied character of stasis bile in cases free of infection. It was found that the gall-bladder and ducts exerted opposite influences upon the bile, the former concentrating and thickening it, while the latter diluted it with a thin, colorless, chocolate-free secretion. In obstructed ducts separated from the gall-bladder, this fluid gradually replaced the small amount of bile originally incarcerated, forming the "white bile" of surgeons. On the other hand, when obstructed ducts connected with an approximately healthy gall-bladder, the stasis fluid is at first a true bile, greatly inspissated by loss of fluid through the bladder wall, darkened by change in pigment and thickened with gall-bladder mucus. Later, duct secretion mixed with the tarry accumulation and gradually replaced it. The writers state that "the concentrating activity of the gall-bladder cannot but be a potent element in the formation of stones," that "intermittent biliary stasis is admitted to be the principal predisposing cause of cholelithiasis; and the stasis is to be thought of as effective, in many instances at least, through the excessive biliary inspissation for which it gives opportunity," so that "a normal gall-bladder can become, merely through functional activity, a menace to the organism." The writers conclude by saying that "in patients with the tendency to stones frequent feedings may lessen the danger of their formation."

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**The Relationship of the Pneumococcus to Acute Infections of the Upper Respiratory Tract in Man. Influenza Studies VI.**—GORDON (*Jour. Infect. Dis.*, 1921, 29, 437) studied the incidence of pneumococci in upper respiratory passages of normal persons and in those suffering from "common colds," epidemic sore-throat and influenza. The material was recovered by swabbing the nasopharyngeal mucosa, seeding in an enrichment medium of 5 per cent sheep-dextrose-blood broth for eight to twelve hours at 37° C. and injecting 1 cc of the broth culture, intraperitoneally, into white mice and the pneumococci were typed from the peritoneal washings by agglutination and precipitin tests in the usual manner. The writer found the average incidence of pneumococcus to be about 21 per cent in normal throats, 35 per cent in common colds and 38 per cent in influenza. Fixed types of pneumococci were infrequent in normal persons and in persons with colds, being more frequent in influenza patients. No serologic relationship could, in general, be demonstrated between the pneumococci found in these infections, while no common strain of pneumococcus was present in acute respiratory infections. In a localized epidemic, a type IV strain was uniformly encountered. The pneumococci isolated from patients with colds and influenza were more virulent than the strains from normal throats.

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**The Gram-negative Cocci in "Colds" and Influenza. Influenza Studies VII.**—By culturing swabs taken from the middle fossa of the nose and nasopharynx in cases of rhinitis and from the nasopharynx and tonsil in those showing inflammatory processes of pharynx, larynx, tonsils and bronchial mucosa, GORDON (*Jour. Infect. Dis.*, 1921, 29, 462) found Gram-negative cocci more frequently in the nasopharynx than the tonsillar region and anterior nares. Three different mediums

were utilized — the vitamine-blood-pour agar plates of Park and Williams, the oleate-hemoglobin agar of Avery, and a 5 per cent sheep broth agar made from a veal infusion base. The writer emphasized the importance of maintaining a high moisture content in the incubator. He also found that the Gram-negative cocci, occurring both in the nose and throat of normal persons and of those suffering from acute upper respiratory infection, may be grouped according to cultural characteristics and fermentative differences. There was no essential difference in the incidence of the various groups in common colds and in normal persons, while in epidemic influenza the incidence was less than in normal individuals. *M. catarrhalis* was the commonest member of the Gram-negative cocci group and could be divided into five subgroups on the basis of cultural differences. This organism, the writer found, constitutes a permanent member of the normal throat flora. Inasmuch as no distinguishable differences in virulence for mice or rabbits could be determined between strains of *M. catarrhalis* from normal sources and those from colds or influenza, the writer concludes that "there is no indication that *M. catarrhalis* is generally concerned in the pathogenesis of common colds or influenza."

**Further Observations on a Rapid Method of Pneumococcus Typing.**— In comparing the results obtained in typing the pneumococcus from the sputum of 100 consecutive cases by the "rapid precipitin method," the Avery method, a modified Avery method (substituting inulin for dextrose and adding Andrade's indicator) and the mouse method, OLIVER (*Jour. Infect. Dis.*, 1921, 29, 518) found that, in all but two instances, a typing of the pneumococcus was effected within from thirty to forty minutes by the rapid method, which was checked by the longer cultural and mouse methods. Of the 100, 33 were Type I; 10 were Type II; 9 were Type III; 28 were Type IV, and 20 were streptococci. The writer states that the substitution of inulin and addition of Andrade's indicator possess certain advantages over the standard Avery method. As given in these columns before, the "rapid precipitin method" consists in centrifuging 1 to 2 cc of the sputum, after making a direct smear, adding 3 to 5 drops of undiluted ox bile (or 10 per cent solution of sodium taurocholate) and sufficient physiologic salt solution to insure fluidity, stirring thoroughly with a glass rod or grinding in a mortar and heating in a water bath at 42° to 45° C. for twenty minutes. Of the centrifugate, 0.3 to 0.5 cc are put into each of three small clean tubes, to which are added 1 or 2 drops of undiluted Types I, II and III pneumococcus antiserum, respectively. A positive precipitin test manifests itself as an almost immediate flocculation, which is enhanced by again heating at 42° C. for from ten to twenty minutes.

**The Occurrence of Hemolytic Streptococci in the Normal Throat.**— Being conversant with the fact that the incidence of hemolytic streptococci in the throats of normal persons, as given by various workers, ranges from ten to sixty per cent or higher, DAVIS, (*Jour. Infect. Dis.*, 1921, 29, 524) obtained surface cultures from the pharyngeal mucosa and palatine tonsils, when present, of 45 individuals, in groups of 15, making three or more examinations at varying intervals, usually

extending over a period of one month. It was found that all, at some time, showed the presence of hemolytic streptococci in the throat, the percentage positive for the different groups varying from 33 to 66. In relation to the other organisms, the number of hemolytic streptococci were few, comprising approximately 1 to 10 per cent of all the colonies that grew. As a rule, the cultures from the 9 tonsillectomized persons of the 45, contained fewer hemolytic streptococci than from those with tonsils.

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## HYGIENE AND PUBLIC HEALTH

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**The Treatment of Leprosy with the Ethyl Esters of Chaulmoogra Oil.**—The Public Health Service (*Public Health Reports*, 1921, 36, 2769) publishes a warning against an over-optimistic estimate of the use of chaulmoogra oil in the treatment of leprosy. It is found that "arrested" cases may relapse, and that about 8 per cent have already relapsed.

**Experimental Mumps Meningitis.**—WOLLSTEIN (*Jour. Exp. Med.*, 1921, 34, 541) has shown that an aseptic meningitis of three to five days' duration and favorable prognosis can be induced in cats by intrathecal injection of sterile saliva filtrate from early cases of parotitis, and that such a meningitis can be transmitted to other cats by injecting the cerebrospinal fluid in the same manner. The cerebrospinal fluid does not at any time contain bacteria which grow with the ordinary culture methods.

**The Basal Metabolism of Infants Fed on Dry-milk Powder.**—TALBOT (*Public Health Reports*, 1922, 37, 116) reports that "infants fed on dry milk powder show either a normal or a slight elevated 'basal' metabolism" together with, in many cases, a slight elevation of temperature.

**A Note on the Natural Immunity of Wild Rats to Plague.**—SPENCER (*Public Health Reports*, 1921, 36, 2836) points out that all previous work on the natural immunity of rats has been done on rats that had been exposed to plague. His own observations were made on rats from a community in which plague had never prevailed and a considerable percentage of these were found to be immune to both cutaneous and subcutaneous inoculations.

**Headache.**—COBB (*Jour. Ind. Hygiene*, October, 1921, 3, 6, 173) states that headache is a common complaint among industrial workers, causing in some units as much as 23 per cent of the cases of lost time and an average of 10 to 15 per cent in the mercantile establishments studied. The causes of headache are many, but, among the employes examined, acute infection, constipation, poor hygiene, psychoneurosis and eyestrain, in the order named, were the commonest. A careful history with interest in personal and occupational problems is essential to diagnosis. The physical examination must be thorough and orderly, with emphasis on the neurological findings, but it need not be time-consuming if carried out according to schedule.

**Experience with Bubonic Plague (Human and Rodent) in Galveston, 1920.**—BOYD and KEMMERER (*Public Health Reports*, 1921, 36, 1754) report a close relationship between human and rodent plague when both the home and the place of employment of the patient were considered. Plague rats were widely scattered, and where the epizootic was recognized early, human cases were prevented. Anti plague serum was used with apparent advantage. One case of laboratory infection at autopsy is recorded. The details of the lesions in infected rats are given. *Leomopsylla cheopis* was found to be the predominant flea. Anti plague measures are credited with bringing the epidemic to an end.

**The Pathogenicity of *B. Abortus* and *B. Melitensis* for Monkeys.**—Recent observations have proved that *B. melitensis* and *B. abortus* are morphologically, biochemically and serologically closely related. In order to demonstrate the real relationship of the two bacteria, it becomes necessary to compare their effects upon animals. The majority of the experiments by early observers on *B. melitensis* were carried out on the monkey. It therefore seemed advisable to FLEISCHNER, VECKI, SHAW and MEYER (*Jour. Inf. Dis.*, 1921, 29, 663) to make similar experiments with *B. abortus*. They found that following an intravenous inoculation of *B. abortus*, agglutinins develop fairly rapidly in the blood of monkeys. The animals may show an intermittent type of fever and lose weight. At postmortem examination it is possible to recover the organisms from the spleen, lymph nodes and liver, while even on the fourth day after the injection the blood stream is found sterile. The authors concluded that virulent strains of *B. abortus* in sufficiently large dosage are pathogenic for monkeys. *B. melitensis* is far more invasive than *B. abortus*. One or two feedings of one-thousandth the amount necessary to cause an infection with *B. abortus* is sufficient in *melitensis* infection to parasitize a monkey.

**Typhus Fever at the Boston City Hospital.**—SHATTUCK (*Boston Med. and Surg. Jour.*, 1922, 186, 235) examined the records of the Boston City Hospital for the past ten years and found that during that period of time 4 cases had been diagnosed as typhus fever. He states that in a few cases diagnosed otherwise, a diagnosis of typhus would probably have been justified. The signs in another small group of cases are highly suggestive of typhus. Numerous cases, probably not typhus, had eruptions suggestive of typhus. Shattuck concludes that it would seem probable that a few cases of typhus fever escaped detection.

The records indicated that the possibility of typhus was not considered in these cases. He states that the diagnosis of typhus is easy in typical cases, but it is important to realize that typhus may simulate a number of other common diseases, and that they in their turn may produce eruptions very suggestive of, or even similar to, that of typhus. The diagnosis of typhus in children is more difficult, as a rule, than in adults, because typhus in children generally runs a very mild course. The diagnosis of typhus in atypical cases may be difficult or impossible by the use of known clinical methods, even when supplemented by the ordinary diagnostic procedures of the laboratory. Two of the newer methods of diagnosis are especially valuable. These are: (a) The proteus reaction of Wilson, Weil and Felix, and (b) microscopic examination of bits of skin excised during life.

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**Report of the Committee on Bathing Places.**—A committee of the AMERICAN PUBLIC HEALTH ASSOCIATION (*Am. Jour. Pub. Health*, 1922, 12, 121) sent out a questionnaire asking physicians to report what diseases they considered might be transmitted in public bathing places and to report cases of whatever disease they had observed in their practice which had been definitely traced or might be traced to water, suits or towels at a bathing place. The answers to this questionnaire brought out a surprising amount of information, which is summarized as follows: The most significant and important information obtained was reports of epidemics of various diseases which may be considered reasonably authentic. Seven different physicians reported epidemics of conjunctivitis, and six others epidemics of skin diseases, 4 of these being epidemics of furunculosis, 2 of impetigo contagiosa, 2 of molluscum contagiosum and 1 of eczema. Two physicians reported epidemics of middle-ear infection which from the history submitted were undoubtedly attributable to infection of the water at the bathing places. Two other physicians reported epidemics of tonsillitis and pharyngitis, and one reported an epidemic of nasal-sinus infection in which all evidence pointed to bathing water as the origin. One of the members of the committee also reported an epidemic of typhoid fever in a camp for boys, which was unquestionably traced to bathing in polluted water.

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**Venereal Spirochetosis in American Rabbits.**—Of 50 rabbits, otherwise regarded as normal, 3 adult females and 2 adult males (10 per cent) were found by NOGUCHI (*Jour. Exp. Med.*, 1922, 35, 391) to have in their genitoperineal region certain papulosquamous, often ulcerating, lesions. A recently purchased group of 20 rabbits was also found to contain 6 females (30 per cent) with similar lesions. Noguchi states that this condition runs a chronic course and is characterized by the presence of a spiral organism closely resembling *Treponema pallidum*. The rabbit spirochete has the same morphological features as *Treponema pallidum*; it is possibly a trifle thicker and longer than the average *pallidum*. Long specimens measuring 30  $\mu$  are frequently encountered, and they show a tendency to form loosely entangled knots. A stellate arrangement of several organisms in a mass is frequently observed. In the lesion of one rabbit there were two types of spirochete, one of the variety just described, the other a somewhat coarser organism, closely resembling *Treponema calligyrum* found in a human condyloma, but a



trifle thinner and longer. This organism is perhaps merely a variant type of the rabbit spirochete. The histological reactions are similar to, but considerably less cellular than, those occurring in typical primary syphilitic lesions. There is a marked hyperkeratosis and interpapillary infiltration, not observed in scrotal chancre. The disease is transmissible to normal rabbits, in which the usual papular lesions can be readily reproduced in the genitoperineal region. In the first passages the incubation period varied from twenty to eighty-eight days; subsequently one of the strains produced a lesion in twenty days on the second, and in five days on the third passage. No typical orchitis or keratitis was produced in the rabbits of the series reported, although in one of the original rabbits scaly, papular lesions developed on the nose, lips, eyelid and paws. Monkeys (*Macacus rhesus*) failed to show any lesions within a period of four months after inoculation. In one instance transmission was accomplished through the mating of an infected female with a normal male. The Wassermann reaction was uniformly negative in the 5 rabbits with spontaneous lesions and in 18 rabbits experimentally infected. Salvarsan had the same therapeutic effect on the lesions produced by the rabbit spirochete as on the experimental *pallidum* lesion of the rabbit. Noguchi concludes that the organism belongs to the genus *Treponema*, and may be designated *Treponema cuniculi*.

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**A Program for the Statistics of the Venereal Diseases.**—DUBLIN (*Public Health Rpts.*, 1921, 36, 3071) states that the statistics of venereal diseases are at the beginning of their development. They have been for the most part descriptive rather than analytic in character. But, elementary as they have been, they have served very materially to develop the campaign of social hygiene. Much still remains to be done in this important field of public health work. The development of the program will require not only a larger mass of accurate and fundamental data but will call for higher methods of statistical analysis than have heretofore been necessary. Special problems of research will tax the ingenuity of the most skilful technicians. The statistician will find more and more opportunity for active coöperation with the practical workers in the field of venereal disease, and the two groups should work more cordially together.

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**Amino-acid Deficiency Probably the Primary Etiological Factor in Pellagra.**—GOLDBERGER (*Public Health Rpts.*, 1922, 37, 462) summarized briefly the important part of the evidence proving diet to be the primary controlling factor in the prevention and causation of pellagra. He states that cases of pellagra are reported that were observed to occur in individuals who were known to have consumed daily, during the period of not less than two and one-half months immediately before the onset of the distinctive eruption, what is judged to have been a liberal supply of mineral elements and the known vitamins, which would indicate that a deficiency of these dietary factors is not essential in the causation of the disease. These factors having thus been excluded, the dominating role of diet in the prevention and causation of pellagra must be referred primarily to the character of the protein (amino-acid) supply, this being the only other dietary factor at present known to be necessary

to physiological well-being. On the assumption that all the dietary factors essential in human nutrition are known, it may be concluded that the essential etiological dietary factor is a specific defect in the amino-acid supply, probably in the nature of a deficiency of some special combination or combinations of amino-acids. There is reason to believe that, besides the specific amino-acid defect, pellagra-producing diets may and probably frequently do have other more or less serious faults, including non-specific amino-acid deficiencies which may operate as accessory etiological factors. In some preliminary therapeutic trials with amino-acids the dermal lesions in each of two cases seemed to show a markedly favorable reaction to cystine; and in a third case a steady gain in weight, with some improvement in diarrhea, accompanied the administration of both cystine and tryptophane.

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**The Effect of Heat on the Calcium Salts and Rennet Coagulability of Cow's Milk**—PALMER (*Proc. Soc. Exp. Biol. and Med.*, 1921, 19, 137) states that when milk is boiled a precipitation of a portion of the calcium phosphates occurs, the amount of fixation being proportional in general to the amount and duration of heat applied. It has been commonly believed also that some fixation of the calcium phosphates takes place during the holding process of pasteurization. The fact that pasteurization of milk retards the coagulability of the casein by rennet, and the fact that this property can be restored by the addition of calcium chloride to the milk, have been presented in support of the view that heat changes some of the soluble calcium salts to an insoluble form. The experimental evidence for such a change is, however, contradictory. Palmer showed that the partial fixation of the calcium salts of milk by pasteurization or boiling is readily explained simply on the grounds of the effect of heat on colloidal solutions of  $\text{CaHPO}_4$ , the calcium phosphate natural to cow's milk. He has shown further that the effect of heat in retarding the rennet coagulability of milk is not related directly to the loss of colloidal  $\text{CaHPO}_4$  because the addition of colloidal  $\text{CaHPO}_4$  to dialyzed milk does not restore its coagulation by rennet, while the addition of  $\text{CaCl}_2$  or  $\text{HCl}$  does restore this property. Palmer discusses briefly the phenomenon of rennet coagulation from the standpoint of the chemical and physicochemical reactions involved, and also from the standpoint of the possible bearing which the addition of calcium salts to heated milk has on this phenomenon.

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**Experiments on Alastrim.**—LEAKE and FORCE (*U. S. Public Health Rpts.*, June 24, 1921) produced a vesicopapular eruption in monkeys by inoculation both with crusts and with vesicle contents from alastrim patients. The animals were protected against reinoculation with alastrim and vaccine virus. Rabbits inoculated with alastrim showed no eruption, but were almost completely immune to vaccine virus. Rabbits previously inoculated with vaccine virus gave positive intracutaneous reactions to smallpox crusts, alastrim material, and vaccine virus, but remained negative to chicken-pox crusts. The authors state that the fact that definite immunity to vaccinia is produced by previous inoculation with alastrim is additional evidence of the essential identity of alastrim with smallpox.

**Malnutrition and Its Relation to Tuberculosis.**—CHADWICK (*Am. Rev. Tuberc.*, 1921, 5, No. 8, 674) made physical examinations of the school children of Westfield, Mass., who were underweight. At the school selected there were 659 pupils. The number of malnutrition cases in this school was 186; 146 of this group were examined and 48, or 33 per cent, were found to be definitely tuberculous. The author states that the average percentage of malnutrition among the 2828 children that make up the school census in nine of the Westfield schools is 32 per cent. If the law of averages holds true, then fully one-third of this number of children suffering from malnutrition have diseased bronchial nodes, which is the first step in the development of pulmonary tuberculosis. Furthermore, 48 cases in one school of 659 pupils is a little over 7 per cent of the entire number. While it is not justifiable to draw too many conclusions from so small a number of children examined, it is significant that this percentage of diseased children coincides closely with the present death rate from tuberculosis, which is not far from 7 per cent. It may be assumed, however, that a large percentage of these 48 children will eventually break down and develop active tuberculosis and many of them will die before they are twenty-five years of age unless they have exceptionally good care and good luck. Antituberculosis activities should be directed more and more toward child welfare. To cover such a vast field and get thousands of tuberculous and potentially tuberculous children under supervision there should be strongly advocated in every city and town the adoption of a method of group instruction and individual treatment along the lines developed by Professor Emerson in his nutrition clinics for delicate children. This can best be done in connection with the schools, as the children are there brought under official control for ten months of each year. Extensive preventive work should be done with these children when they are in the earliest stage of disease and at a period in their lives when they will respond most quickly to rational changes in diet and habits of living. The physique must be improved, and strong disease-resisting bodies built up during childhood. Then the cases of tuberculosis, that smoulder away during adolescence only to break forth later on and decimate the ranks of young manhood and womanhood, will become fewer and fewer, and as a cause of death in the next generation this disease will become a much less important factor.

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